Rh(III)-Catalyzed Alkene Difunctionalization for the Synthesis of Nitrogen-Containing Compounds

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Abstract

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Nitrogen-containing compounds are essential structural units in a myriad of biologically active molecules including pharmaceuticals. Although numerous synthetic methods have been developed over the last few decades, new methods constructing them in an efficient way from readily accessible starting material are still great of interest. As a coupling partner of the reaction, alkenes are abundant, general, and therefore ideal starting materials to synthesize a variety of complex, value-added products. In this thesis, we have utilized Rh(III) catalysis to develop efficient synthetic methodologies for nitrogen-containing compounds using alkenes as coupling partners. In Chapter 2, we developed a unique disconnection approach to pyrrolidines using α-olefins as a 4-carbon source and hydroxylamine derivatives as a nitrogen source of the reaction. In Chapter 3, regio- and diastereoselective synthesis of α,β-unsaturated-δ-lactams from acrylamide and unactivated alkenes initiated from C-H activation are discussed. In Chapters 4 and 5, three-component alkene difunctionalization of alkenes delivering acyclic aminated products including α-amino acids are described.

Table of Contents

List of Charts, Graphs, Illustrations

Acknowledgments

First, I would like to thank my advisor Prof. Tomislav Rovis for accepting and letting me be part of this amazing group. Tom gave me the freedom to pursue my interests while leading me in the right direction, motivated me to love chemistry, helped me to become a better chemist. Under his guidance, I could enjoy every moment of my time in the Rovis group even when the research was not going well. I would also like to thank my committee members Prof. Norton, Prof. Leighton, Prof. Owen, and Prof. Diao for serving on my committee. I look forward to all of our future insightful discussions.

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I also want to thank all the former and current group members for fostering and maintaining a wonderful group culture. I feel incredibly fortunate to have met such great friends and chemists and I consider all of you as family. I wouldn't have achieved any of this without your mentorship, constructive criticism, challenges, suggestions, and friendship.

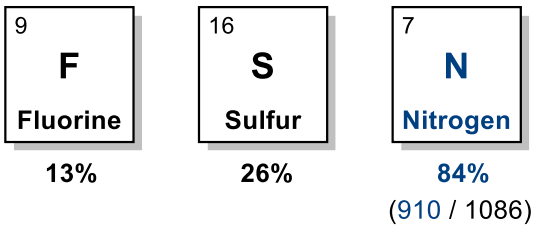
Dedication

To mom, dad, and Sun.

Chapter 1: An Introduction to the Synthesis of Nitrogen-Containing Heterocycles

1.1 *N*-heterocycles in FDA approved drugs

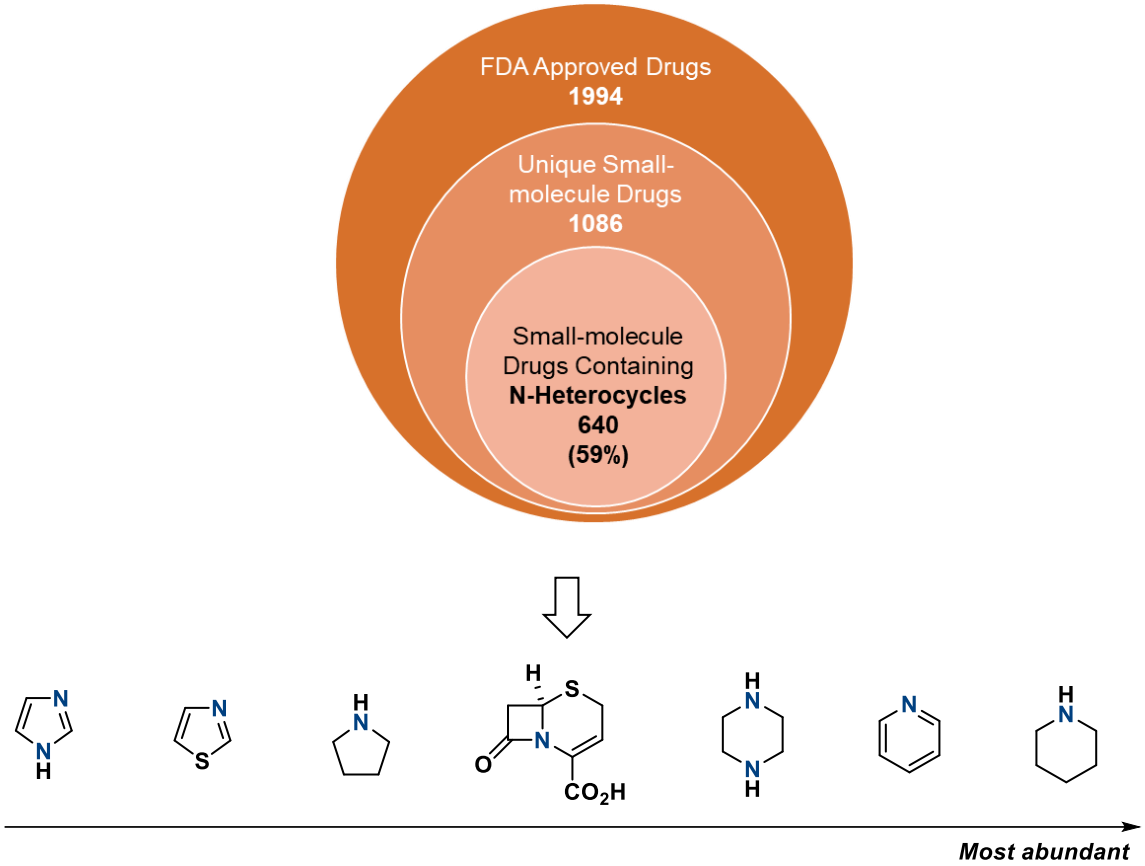
Nitrogen-containing organic molecules are ubiquitous in a myriad of biologically active compounds including natural products, nucleic acids, proteins, and pharmaceuticals. An in-depth analysis of FDA-approved drugs reported in 2014 reveals that among the 1086 unique small-molecule drugs, 910 (84%) contain at least one nitrogen atom far surpassing the numbers for sulfur (26%) and fluorine (13%) (**Scheme 1.1**).[1] Nitrogen is the most commonly observed element in FDA-approved drugs except C, H, and O and numerous blockbuster drugs contain nitrogen in their structures.



Scheme 1.1: Frequency of elements in FDA-approved drugs.

Among these unique small molecule drugs containing nitrogen, around 60% of them possess at least one nitrogen-containing heterocycles (**Scheme 1.2**).[1] Piperidine is the most commonly observed *N*-heterocycles, followed by pyridine, piperazine, cephem, and pyrrolidine, etc. Even though it is exceedingly difficult to identify the single reason why nitrogens are prevalent in drugs due to the large diversity of their function in our biological system, in general, nitrogen heterocycles accept or donate a proton readily, form diverse weak interactions such as hydrogen

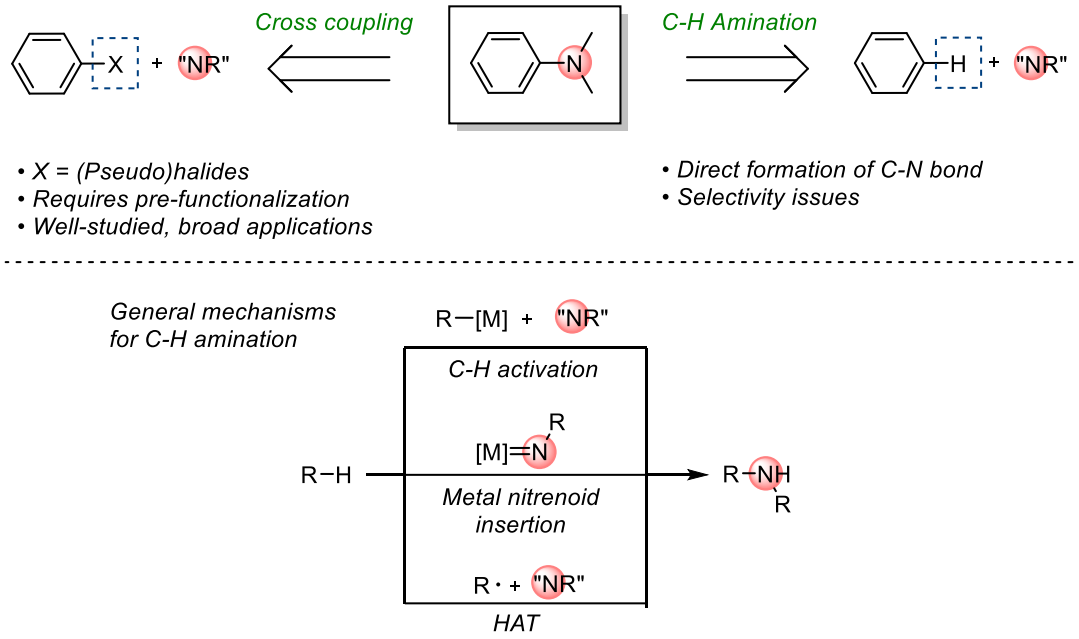
bonding, dipole interactions, etc., which allows them to bind with a variety of enzymes and receptors in biological targets with high affinity.[1-3] Although significant efforts have been devoted to the development of synthetic methodologies for nitrogen-containing heterocycles over the last few decades, developing efficient routes to them with easily accessible starting material is still of great interest from both industry and academia.



Scheme 1.2: Nitrogen-containing heterocycles in FDA-approved drugs.

1.2 Transition metal-catalyzed C-H aminations

The importance of the nitrogen heterocycles has motivated synthetic chemists to develop a new way of constructing them. Especially, transition-metal catalysis has played an essential role in the progress of the field since it provides unique and efficient routes to form a new carbon-nitrogen bond.[4, 5] In this context, one of the classical methods to build a C-N bond is through cross-coupling reactions such as Ullman reaction with Cu catalyst[6] or more recently developed Pd-catalyzed Buchwald-Hartwig reaction[7] to give aniline derivatives (**Scheme 1.3**).



Scheme 1.3: Transition metal-catalyzed C-H aminations.

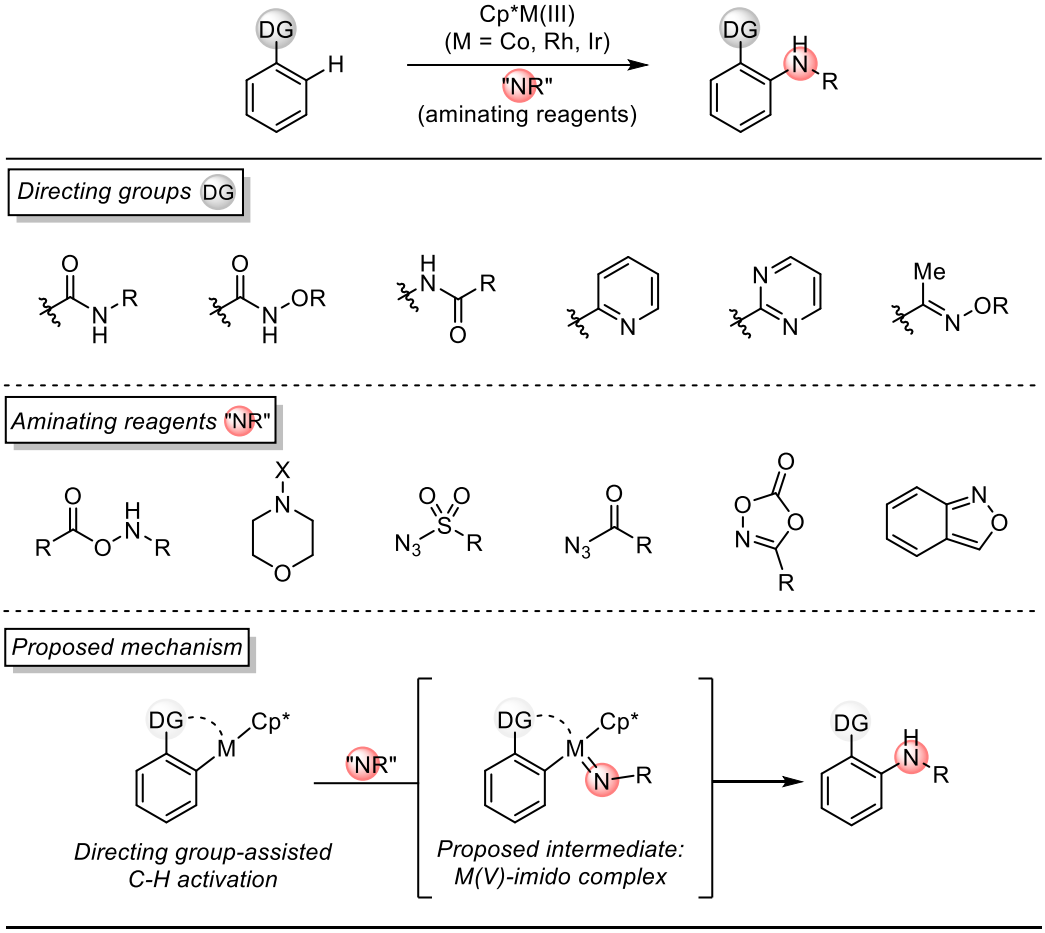
Such cross-coupling reactions between aryl (pseudo)halides and amines are well-studied, and, are widely used in a variety of research fields including medicinal chemistry. However, the reaction requires pre-functionalized substrates as coupling partners of the reactions and inherently generates halide salt as a side product. Alternatively, the direct functionalization of inert and

ubiquitous C-H bonds has received great attention (**Scheme 1.3**). Compared to cross-coupling reactions, the biggest advantage is the rapid access to value-added amine products from readily accessible substrates although this approach invokes the selectivity issue when multiple C-H bonds are electronically and sterically similar.

The mechanism of transition metal-catalyzed C-H amination can be categorized into three different classes (**Scheme 1.3**).[5, 8-11] First, a transition metal catalyst "activates" the C-H bond in a molecule and the resulting organometallic complex subsequently reacts with an external nitrogen source to give the desired amination product. Second, the metal catalyst generates a metal-nitrenoid intermediate that undergoes outer-sphere C-H insertion to form a C-N bond. Last, photoredox catalysis has been utilized to generate a radical intermediate through the hydrogen atom transfer and the resulting radical reacts with nitrogen source to give an aminated product.

1.3 C-H aminations with Cp* group 9 metal catalysis

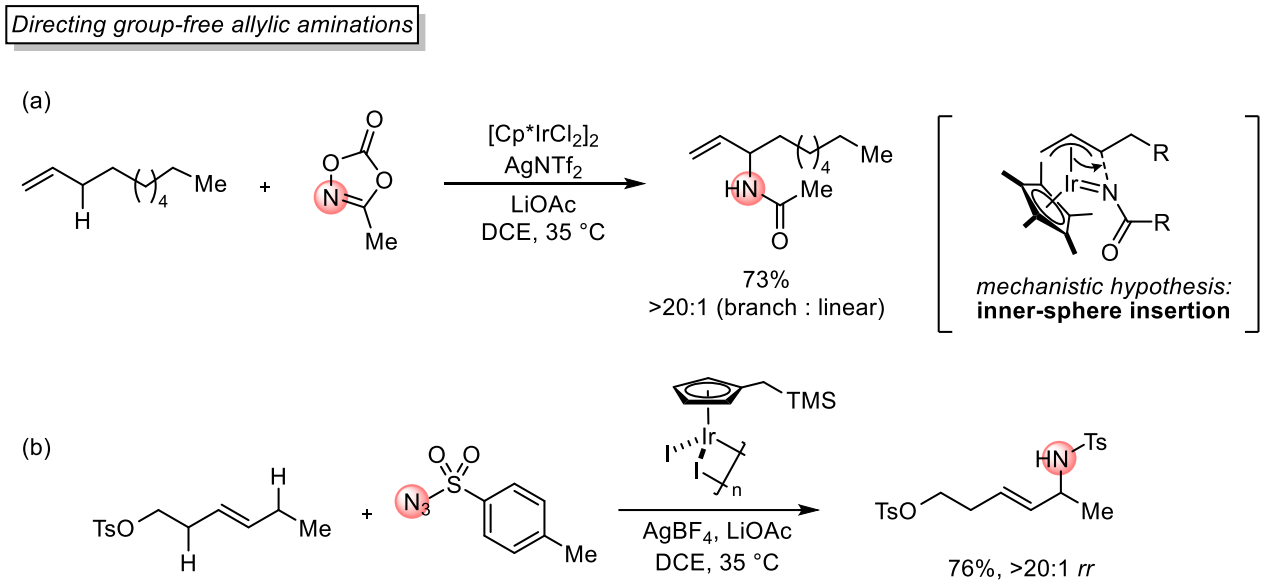
As mentioned above, one of the challenges of C-H functionalization is the selectivity due to the presence of multiple indistinguishable C-H bonds in a molecule. One solution to this problem is using a functional group that can coordinate to the metal center, then the metal complex undergoes selective C-H activation on the basis of proximity. Numerous first and second-row transition metal complexes including Pd, Cu, Fe, Mn, and Ru, etc. have been developed to achieve this transformation.[12] For Cp* group 9 metal catalysis, several directing groups have been also utilized for the C-H amination chemistry with a variety of aminating reagents (**Scheme 1.4**).[4] As a key intermediate of the reaction, Cp*M(V)-imido complexes were proposed. Although this intermediate has never been isolated or detected yet, computational studies support Cp*M(V)-nitrene formation as a favored pathway during the transformations.[13, 14]



Scheme 1.4: Cp*M(III) catalysis for directing group-assisted C-H amination.

While the directing group-assisted C-H amination provides excellent chemoselectivity, the installation and/or removal of often unnecessary directing groups limits its synthetic application. As a part of efforts to develop directing group-free C-H amination with Cp* group 9 metal catalysis, In 2019, Rovis group reported Ir(III)-catalyzed branch selective allylic amination of α-olefins (**Scheme 1.5a**).[15] Slightly after this report, Glorius and Blakey groups also reported the same transformation independently.[16, 17] Again, the key intermediate was Ir(V)-imido complexes that undergo C-N bond formation. Later, we expanded this chemistry to more challenging internal

alkenes (**Scheme 1.5b**) that contain almost indistinguishable allylic C-H bonds to achieve site-selective allylic amination.[18]



Scheme 1.5: Selective allylic amination of alkenes.

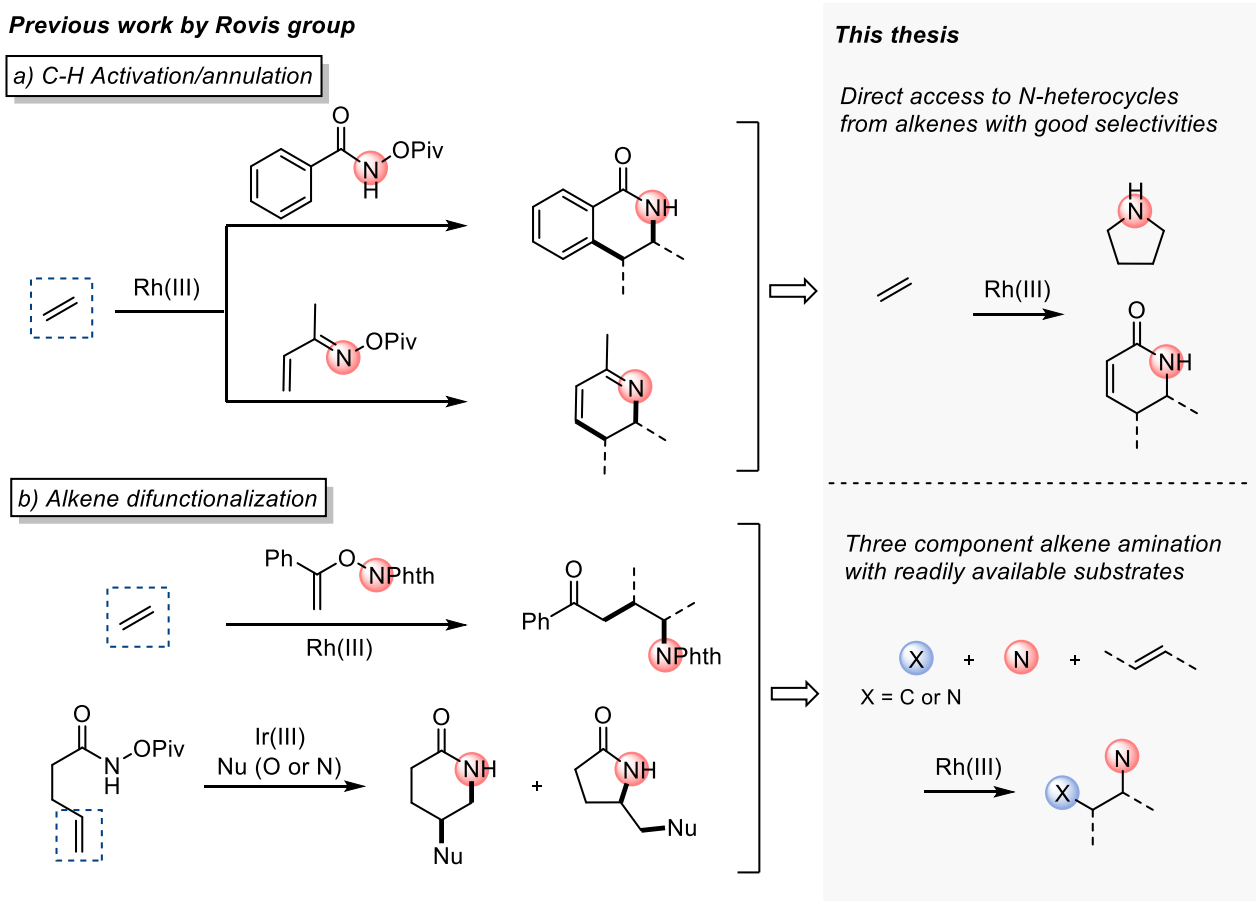
1.4 Alkene aminations with Cp* group 9 catalysis

Previously, Rovis group utilized the Rh(III)-catalyzed C^{sp2}-H activation/annulation strategy for the synthesis of a variety of nitrogen-containing heterocycles with alkenes as coupling partners (**Scheme 1.6a**).[19] The general mechanism of these transformations is Rh(III) catalyst activates a C^{sp2}-H bond through concerted-metalation-deprotonation (CMD), the resulting rhodacycle undergoes migratory insertion with an alkene and subsequently forms a C-N bond to deliver a cyclized product.

In addition to *N*-heterocycle syntheses, we also reported Rh(III)-catalyzed stereospecific *syn*-carboamination of activated alkenes that give acyclic aminated products.[20] As a part of the

alkene difunctionalization chemistry, more recently we published Ir(III)-catalyzed regio-divergent synthesis of γ- and δ-lactams through intramolecular diamination and oxyamination.[21, 22]

As an extension of this previous work mentioned above, in this thesis, Rh(III)-catalyzed alkene difunctionalization for the synthesis of *N*-heterocycles such as pyrrolidines (Chapter 2), α,β-unsaturated-δ-lactams (Chapter 3), and carboamination (Chapter 4) and diamination (Chapter 5) that provides acyclic aminated products will be discussed.



Scheme 1.6: Alkene difunctionalization for the synthesis of nitrogen-containing compounds.

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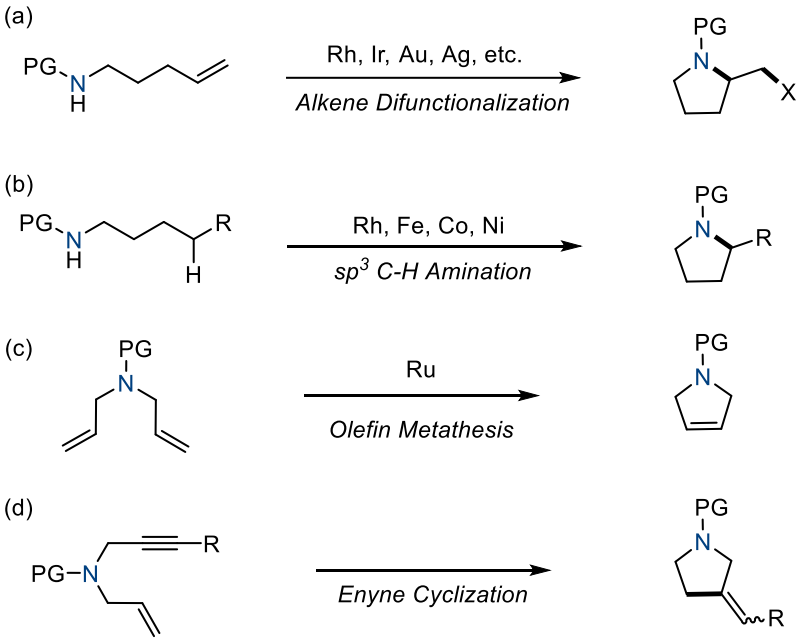
Chapter 2: A Formal [4+1] Approach to Pyrrolidines from Unactivated Terminal Alkenes and Nitrene Sources

2.1 Current methods for pyrrolidine synthesis

Pyrrolidine is a prevalent structural unit in biologically active molecules such as pharmaceuticals and natural products. According to an analysis conducted in 2014 by Njardarson *et al*.,[1] pyrrolidine is one of the top 5 nitrogen-containing heterocycles in FDA-approved drugs, and the most commonly observed 5-membered nitrogen heterocycle. It is also the structural core of various organocatalysts including proline analogs that enable important synthetic transformations.[2-5] Not surprisingly, significant efforts have been devoted to the development of efficient routes to pyrrolidines and early examples can be traced back to the classical Hofmann−Löffler−Freytag reaction in the 19th century.[6, 7] Since then, a myriad of intramolecular cyclization methods has been developed for the synthesis of this saturated 5-membered nitrogen heterocycle. A SciFinder search on pyrrolidine cyclization involving three different disconnections results in more than 5 million reactions, which emphasizes the importance of this structural unit and a diversity of approaches to this heterocycle.

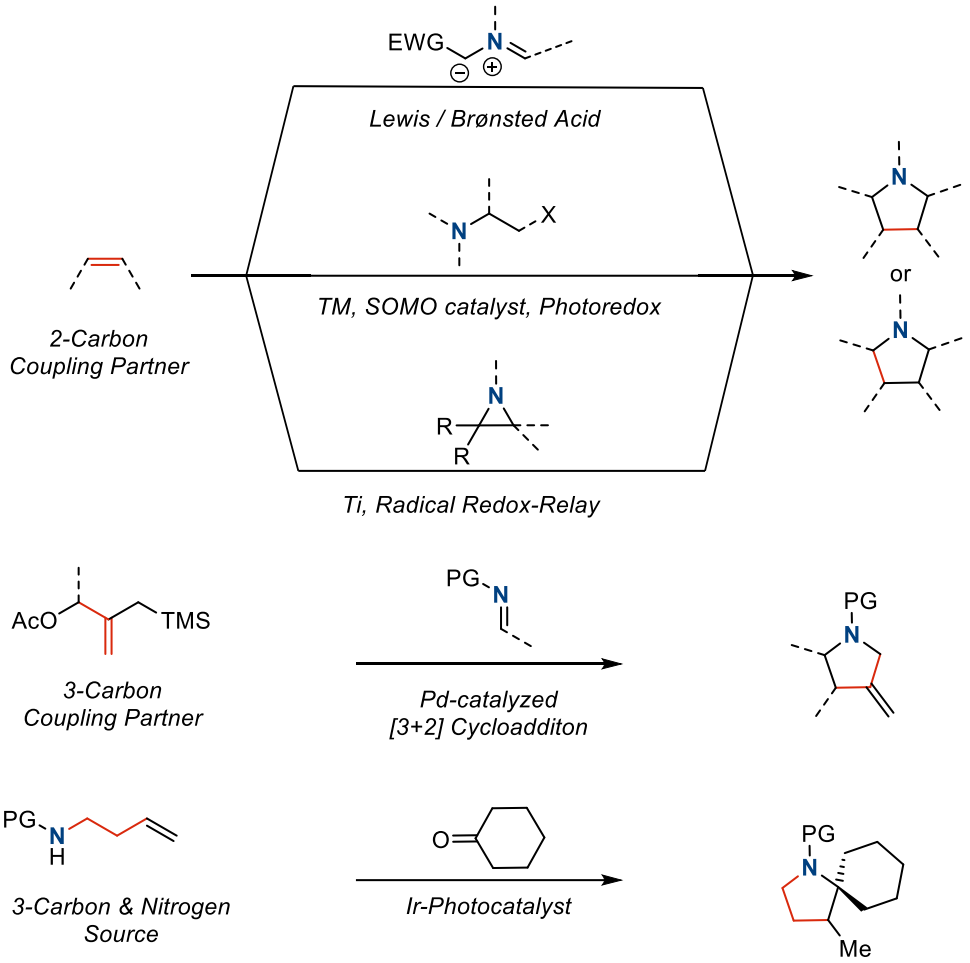
For the recent progress of the field, intramolecular alkene difunctionalization with tethered amine nucleophile is one of the well-established ways of constructing a 5-membered nitrogen ring with various transition metal catalysts.[8] (**Scheme 2.1a**). Recently, Knowles group also utilized photoredox catalysis to achieve this transformation through a proton-coupled electron transfer (PCET) mechanism.[9] Alternatively, intramolecular amination of sp^3 C-H bond through metal nitrene insertion with Rh, Fe, Co, and Ni have been reported for the synthesis of pyrrolidines (**Scheme 2.1b**).[10-13] Although the reactions deliver saturated pyrrolidine derivatives, the disconnection of C3-C4 bond of pyrrolidine is also well-studied and olefin metathesis or 1,6-enyne

cyclization can be categorized into this approach (**Scheme 2.1c** and **2.1d**).[14, 15] While all of these reactions mentioned above are efficient approaches to pyrrolidines with interesting reaction mechanisms, they require the preparation of acyclic precursors before the cyclization that might need multi-step syntheses.



Scheme 2.1: Intramolecular cyclization methods.

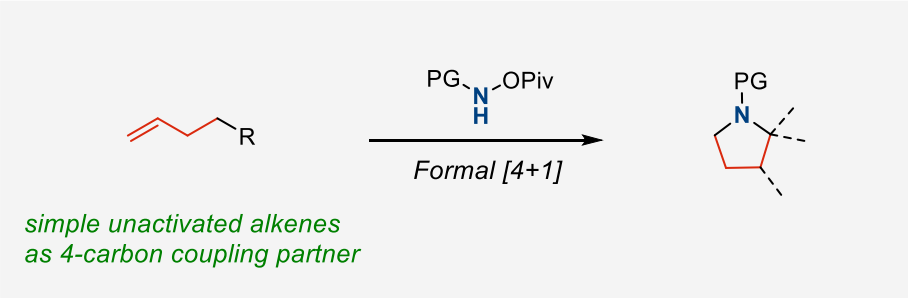
Alternatively, intermolecular, convergent synthetic strategies involving two or three unique components have also received great attention. Among potential reaction partners, olefins are perhaps the most abundant, general, and desirable. For the synthesis of pyrrolidines, alkenes are most frequently used as two carbon sources of the reaction and the [3+2] cycloaddition between azomethine ylides and alkenes represents a well-studied method among them (**Scheme 2.2**).[16-18] Other recent examples also include the reaction of β-amino aldehydes, protected cinnamyl amines, and aziridines with various types of alkenes as two-carbon sources.[19-23]



Scheme 2.2: Intermolecular approaches using alkenes as coupling partners.

Strategies utilizing alkenes as three-carbon coupling partners are relatively rare and often require pre-functionalization. For example, 2-((trimethylsilyl)-methyl) allyl acetate has been reported as a three-carbon source for the palladium-catalyzed formal [3+2] cycloaddition with imines (**Scheme 2.2**).[24-26] Most recently, a visible light-mediated photoredox catalyzed synthesis of spiro-pyrrolidines was reported using homoallylic amines as 3-carbon/1-nitrogen sources with aliphatic ketones as 1-carbon partners.[27] Until we developed this method,[28] the synthesis of pyrrolidines using alkene as a 4-carbon source of the reaction was unprecedented. Such a strategy

would be complementary to current methods with the advantage of providing direct access to pyrrolidines from easily accessible terminal olefins.

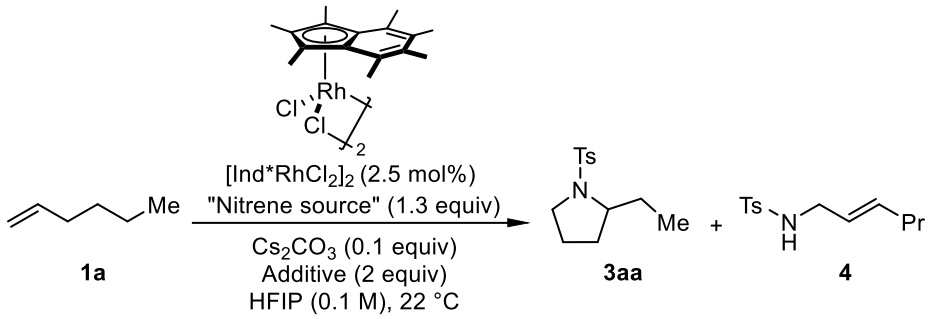


Scheme 2.3: Formal [4+1] approach to pyrrolidine using alkenes as 4-carbon sources.

2.2 Reaction development

We serendipitously discovered this reactivity during the development of two separate research projects. I was trying to develop Rh(III)-catalyzed diamination of unactivated alkenes using 1-hexene (**1a**), and a former group member Dr. Honghui Lei was investigating the mechanism of allylic amination with α-olefins.[29]

Surprisingly, we noted that heptamethylindenyl (Ind*) Rh(III) catalyst[30] delivers the pyrrolidine side product (**3aa**) and linear allylic amination product (**4**) in low yield from 1-hexene (**1a**) and *N*-pivalolyloxy tosylamide (**2a**) (**Table 2.1**, entry 1). Inspired by this preliminary result and the rapid access to pyrrolidines, we sought to optimize the transformation. Although desired product could be formed by Rh(III) alone, we found that the yield of pyrrolidine (**3aa**) is greatly improved by pre-stirring the reaction mixture until full consumption of 1-hexene (**1a**) and then subjecting the reaction mixture with AgOTf at 80 °C (entry 2). Systematic examination of acid additives revealed that $Sc(OTf)_3$ is more effective than AgOTf, promoting the cyclization even at room temperature (entry 3).



1a **3aa** **4**

entry	"Nitrene source"	Additive	yield of **3aa** (%)[a]	yield of **4** (%)[a]
1[b]	Ts-NH-OPiv (**2a**)	-	15	15
2	Ts-NH-OPiv (**2a**)	AgOTf	0 (50)[c]	-
3	Ts-NH-OPiv (**2a**)	$Sc(OTf)_3$	45 (58)[c]	-
4	Ts-NH-OPiv (**2a**)	TfOH	**66**	-
5[d]	Ts-NH-OPiv (**2a**)	TfOH	15	-
6	3-phenyl-1,4,2-dioxazol-5-one	TfOH	0	-
7	Ts-N_3	TfOH	0	-

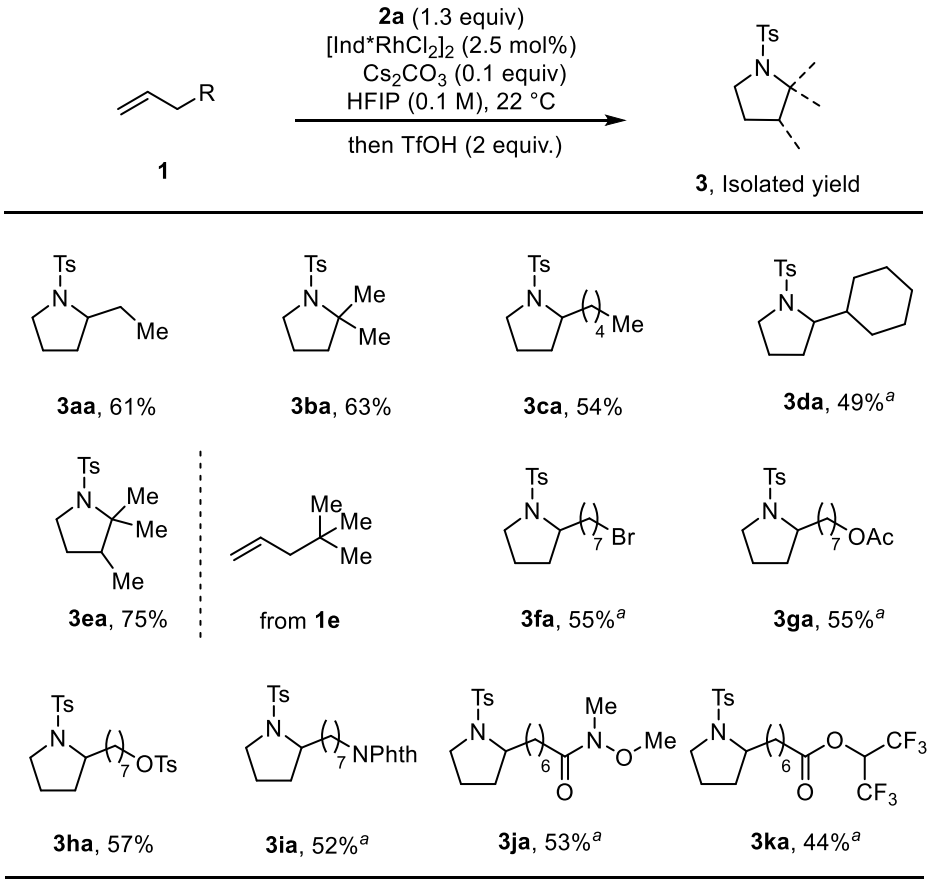
Reactions were conducted on a 0.1 mmol scale using **1a** (1.0 equiv). Additive was added after 24 h. [a]Determined by analysis of ^{1}H nuclear magnetic resonance (NMR) of the unpurified reaction mixture. [b]Reaction was conducted at 40 °C with 1 equiv of **2a**, with $[Ind^*RhCl_2]_2$/AgOTf as the catalyst precursor. [c]Temperature increased to 80 °C after addition of the additive. [d]$[Cp^*RhCl_2]_2$ was used.

Table 2.1: Reaction optimization.

Eventually, TfOH was chosen as an optimal additive, delivering 66% yield of desired 2-ethyl-1 tosylpyrrolidine (**3aa**) (entry 4). The electron-deficient heptamethylindenyl (Ind*) ligand on the Rh(III) catalyst is crucial with the more common $[Cp^*RhCl_2]_2$ providing product in a much lower yield (entry 5).[31] Moreover, other nitrene precursors previously used for the amination chemistry with Cp* group 9 catalysis such as dioxazolone or tosyl azide (entry 6, 7) lead to no pyrrolidine product formation.

2.3 Alkene substrate scope

We next sought to examine the scope of this method with various terminal alkenes (**Scheme 2.4**). The reaction proceeds smoothly with alkenes containing substituents at C4 and C5 positions, giving desired products (**3aa**−**3da**) in good yield. Interestingly, in the case of 4,4-dimethyl-1-pentene (**1e**) where the C4 position is blocked, one of the methyl groups migrates to the C3 position, forming 2,2,3-trimethyl-1-tosylpyrrolidine (**3ea**) selectively. Additionally, a variety of functional groups such as −Br, −OAc, −OTs, −NPhth, −$CONR_2$ and −CO_2R are tolerated when located far from the reaction center, providing corresponding products (**3fa**−**3ka**) in moderate to good yield.

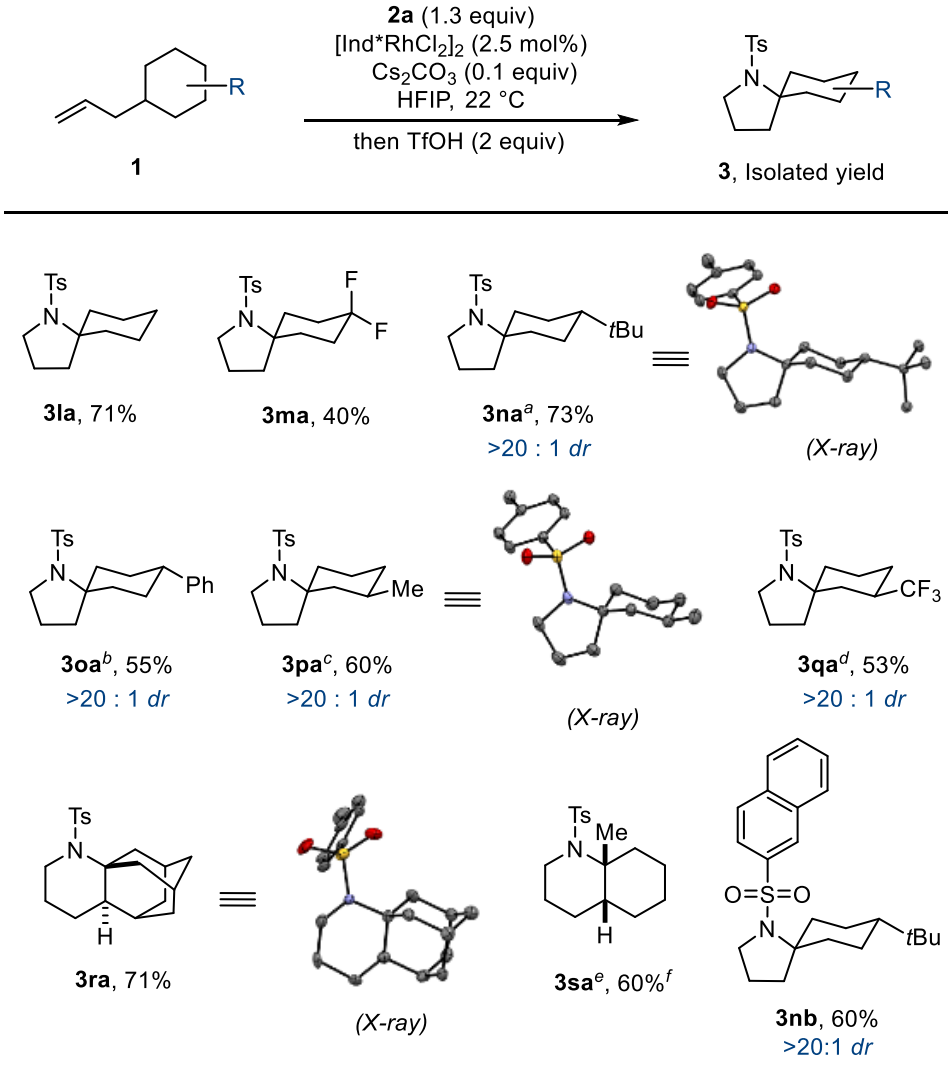


[a]Reaction conducted at 40 °C.

Scheme 2.4: Linear alkene substrate scope.

The presence of proximal nucleophilic functional groups leads to their interception of the cationic intermediates formed in the reaction. For example, benzyl hexenyl ether forms amino methyl tetrahydropyran in good yield under these reaction conditions.

In consideration of the importance of spirocyclic pyrrolidines among pharmaceuticals, we tested synthetic utility of this method for the synthesis of spiro-pyrrolidines with a variety of allyl cyclohexane substrates (**Scheme 2.5**).

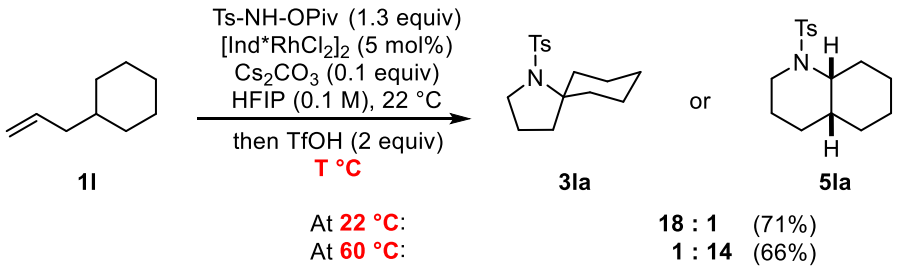


[a]From **1n** (3.1:1 dr). [b]From **1o** (2.8:1 dr). [c]From **1p** (3.0:1 dr). [d]From **1q** (3.8:1 dr). [e]From **1s** (1.6:1 dr). [f]Reaction conducted at 4 °C.

Scheme 2.5: Allyl cyclohexane substrate scope.

Allyl cyclohexane (**1l**) was successfully converted to the 1-tosyl-1-azaspiro[4.5]decane (**3la**) product in excellent yield. A conformational bias in the cyclohexane ring (4-*tert*-butyl, 4-phenyl, 3-methyl and 3-trifluoromethyl) produced corresponding spiro-pyrrolidine products with excellent diastereoselectivity (**3na**, **3oa**, **3pa**, and **3qa**). It is also worth noting that >20:1 diastereoselectivities are achieved regardless of the trans/cis ratio of the starting cyclohexane. The relative stereochemistry of **3na** and **3pa** was unambiguously determined by X-ray crystallography.

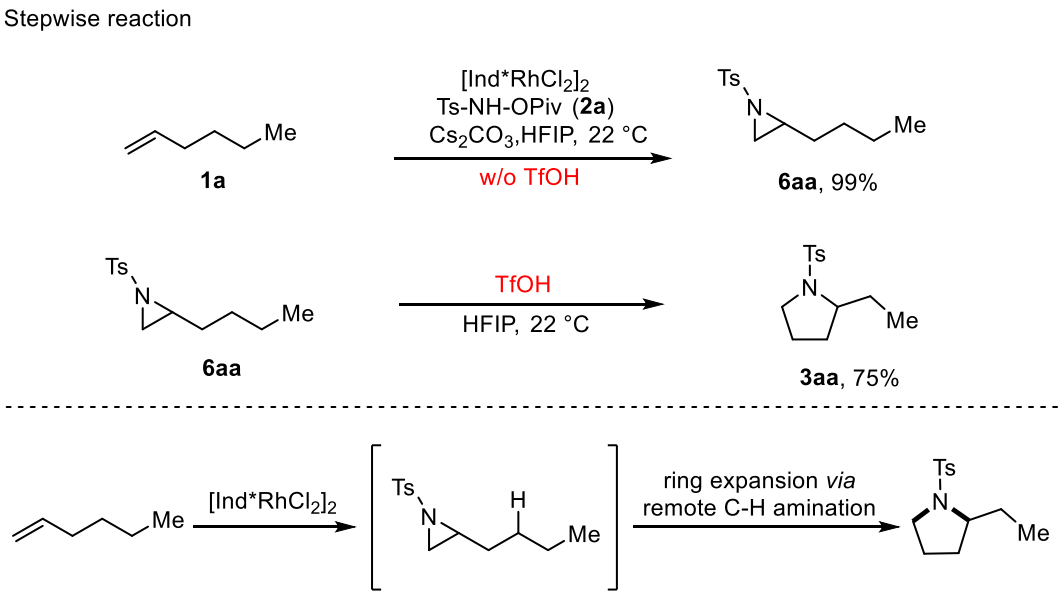
Interestingly, the reaction with 2-allyl adamantane (**1r**) causes a 1,2-hydride shift before cyclization, leading to the formation of an unprecedented structure **3ra**. A similar hydride shift event was also observed with 1-allyl-2-methylcyclohexane (**1s**), giving rise to 6,6-fused bicyclic, decahydroquinoline (**3sa**). Moreover, naphthyl sulfonyl group was introduced as an alternative tosyl protecting group due to its milder deprotection conditions (**3nb**). Last, regiodivergent synthesis of pyrrolidine-based spirocycle (**3la**) and fused bicyclic compound (**5la**) was achieved from allyl cyclohexane (**1l**) with exquisite selectivity by simply changing reaction temperature (**Scheme 2.6**). As a control experiment, we subjected **3la** to triflic acid at elevated temperature (60 °C) and as a result, we observed that **3la** was converted to **5la** which suggests **5la** is formed from **3la** and the final C-N bond formation step is reversible at a higher temperature.



Scheme 2.6: Regiodivergent synthesis of spirocyclic and fused bicyclic compound.

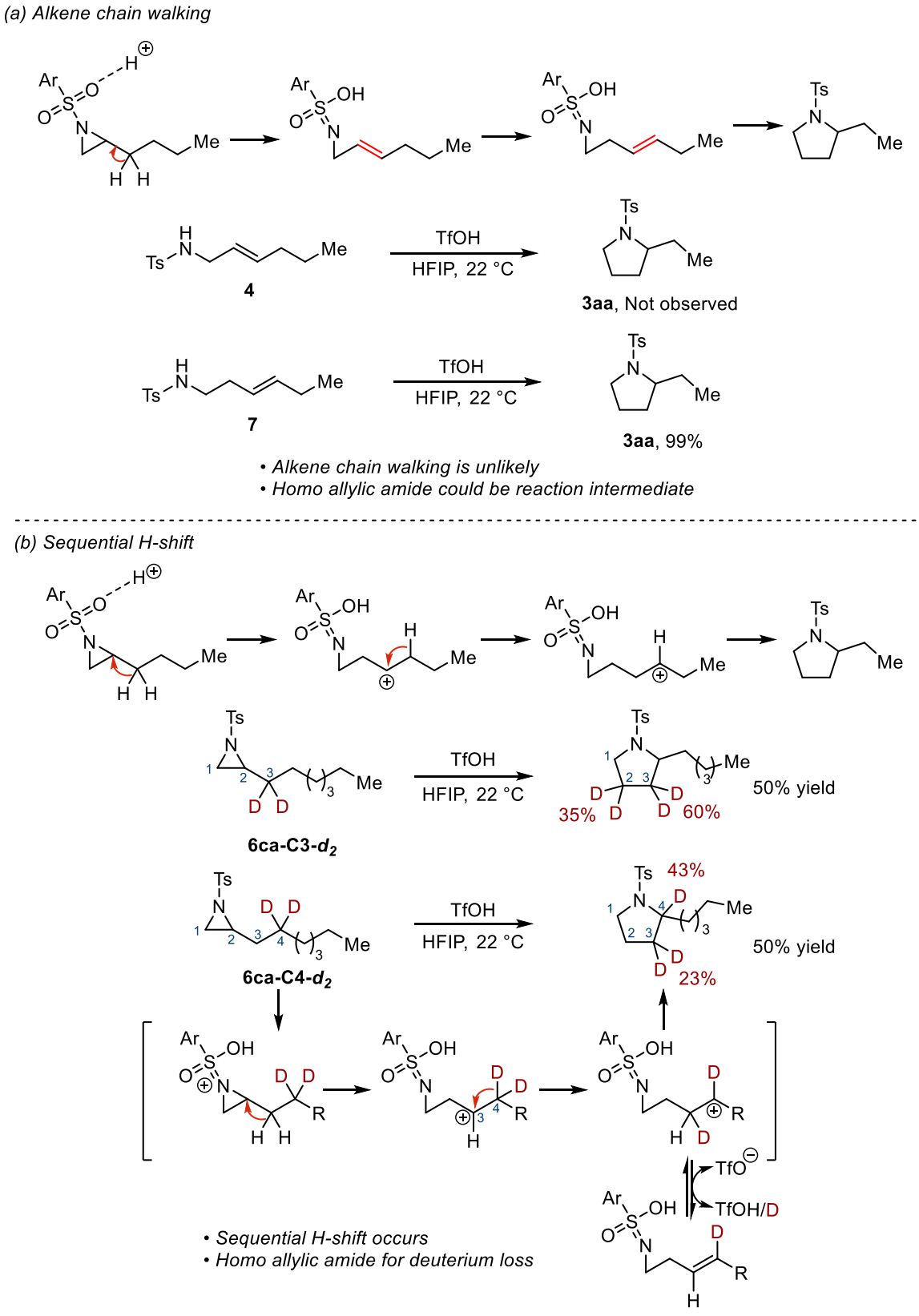
2.4. Mechanistic investigation

To obtain mechanistic insights, we first conducted the reaction with 1-hexene (**1a**) using the standard reaction conditions without the sequential treatment of TfOH (**Scheme 2.7**). As a result, *N*-Tosyl aziridine (**6aa)** was isolated in quantitative yield. Further subjecting the resulting aziridine (**6aa**) to TfOH leads to pyrrolidine product in 75% yield (**3aa**). These results suggest that the Rh(III)-catalyzed intermolecular aziridination of the alkene and subsequent acid-promoted ring expansion is likely responsible for the reaction mechanism.



Scheme 2.7: Mechanistic investigation.

The aziridination of unactivated alkenes catalyzed by Ind*Rh(III) is unprecedented, although it is a well-explored research area. The unexpected and novel part of the reaction mechanism is the ring expansion from aziridine to pyrrolidine through remote C-H amination. Initially, we considered two possible pathways (**Scheme 2.8**).



Scheme 2.8: Mechanistic investigation on aziridine ring expansion.

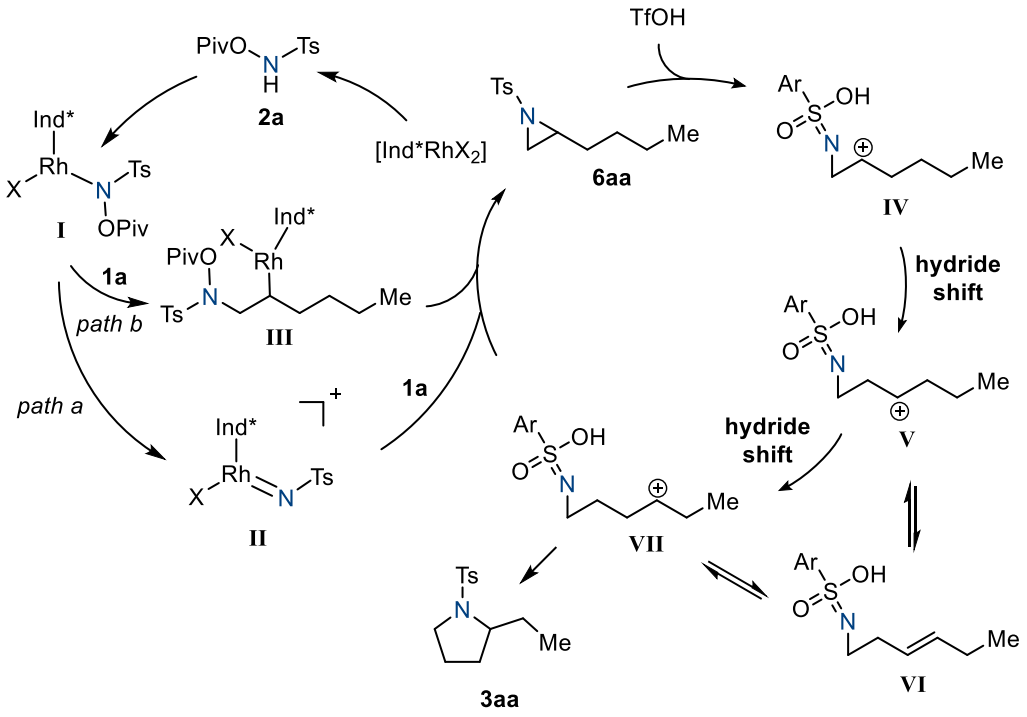
First, the aziridine ring is opened by forming allylic tosylamide and undergoes the alkene chain walking presumably through protonation/elimination pathway. Then, homoallylic tosyl amide will be cyclized to give pyrrolidines in acidic condition. In order to test this mechanism, allylic and homoallylic tosyl amides (**4** and **7**) were prepared and subjected to TfOH (**Scheme 2,8a**). Allylic amine (**4**) does not lead to pyrrolidine product, while a quantitative yield was achieved from homoallylic amine (**7**). These experiments indicate that the alkene chain walking mechanism is unlikely although homoallylic tosyl amide could be one of the reaction intermediates.

The second pathway that we considered was the sequential hydride shift mechanism. To test this idea, we conducted deuterium labeling experiments with C3 and C4 deuterated aziridines (**Scheme 2,8b**, for C1 and C2 deuterated aziridines, see Appendix A). In the case of C3 deuterated aziridine (**6ca-C3-*d*$_2$**), extensive deuterium incorporation is observed at the C2 position which suggests the aziridine ring-opening is initiated by 1,2-hydride shift. The reaction with C4 deuterated aziridine (**6ca-C4-*d*$_2$**) also shows deuterium migration from C4 to C3 position with the significant erosion of deuterium that can be attributed to the formation of homoallylic tosyl amide.

2.5 Proposed mechanism

Taken together, these experiments suggest a plausible reaction mechanism (**Scheme 2,9**). *N*-Pivalolyloxy tosylamide (**2a**) first coordinates to the Rh(III) catalyst and undergoes Rh-nitrene formation (**II**). Alkene aziridination proceeds subsequently to form *N*-tosyl aziridine (**6aa**). It is also possible that the aziridine (**6aa**) is formed through the alkene migratory insertion of intermediate **I**, followed by a concerted C−N bond formation and N−O bond cleavage. Upon treatment with triflic acid, aziridine ring expansion is initiated by 1,2-hydride shift, followed by a

combination of 1,2-hydride shift and elimination/protonation pathways, and eventually quenches the carbocation at C4 position to form the pyrrolidine product (**3aa**). The possible intervention of homoallylic amide **VI** explains the modest loss of deuteration in the deuterium labeling experiments noted above.



Scheme 2.9: Proposed mechanism.

2.6 Summary

In summary, we have developed a Rh(III)-catalyzed formal [4+1] synthesis of pyrrolidines from readily available unactivated alkenes. Mechanistic studies show that the reaction proceeds through a Rh(III)-catalyzed aziridination of the alkene and subsequent ring expansion from aziridine to pyrrolidine promoted by the acid. This method offers a new strategy for pyrrolidine

synthesis by employing a simple alkene as a four-carbon source. With this method, various types of pyrrolidines, especially spiro-pyrrolidines, were rapidly constructed.[28]

2.7 Reference

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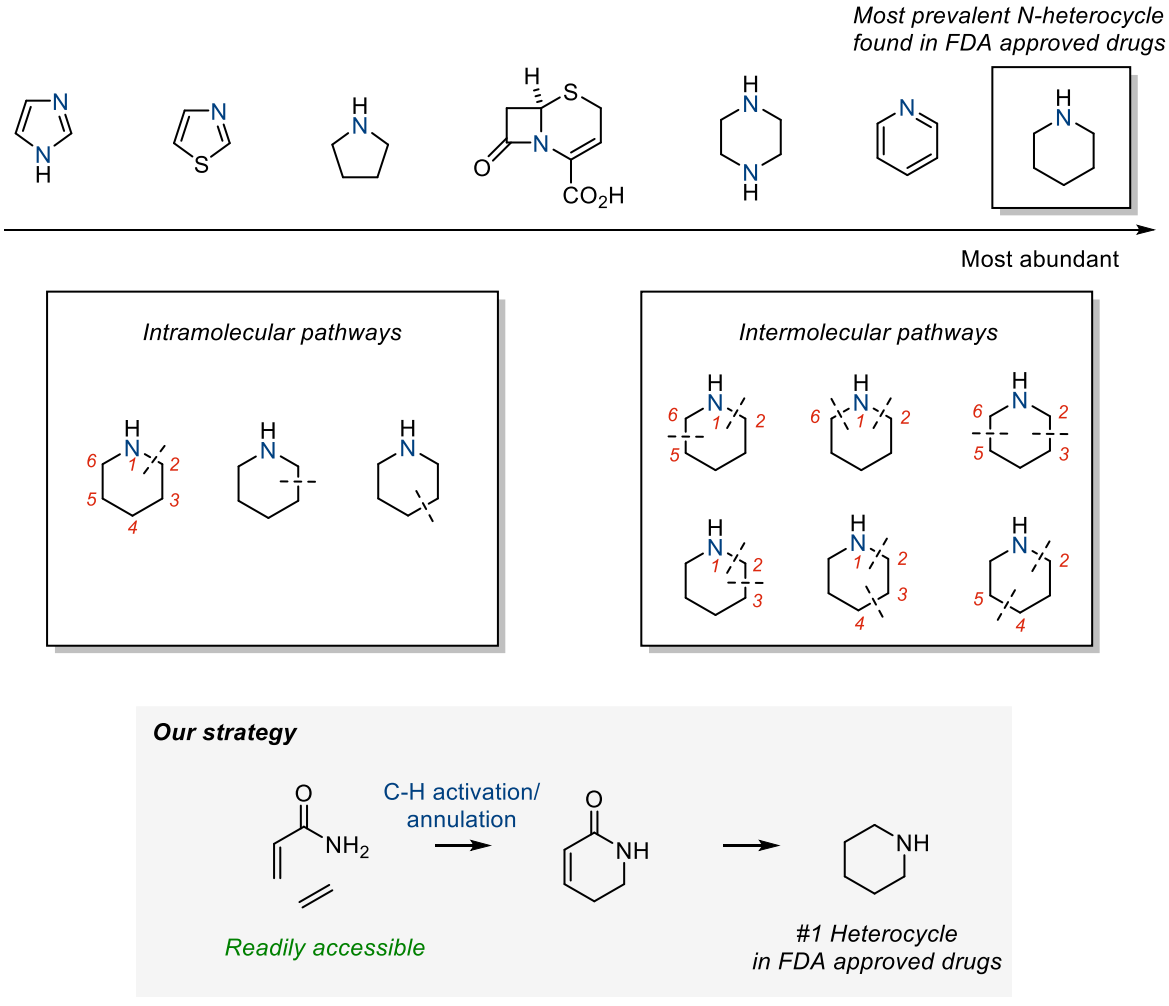
Chapter 3: Direct Regio- and Diastereoselective Synthesis of δ-Lactams from Acrylamides and Unactivated Alkenes

3.1 Introduction

Nitrogen heterocycles are an essential structural unit found in a variety of biologically active molecules. FDA-approved drug analysis shows that around 60% of unique small molecule drugs contain at least one nitrogen heterocycle.[1] Among them, the piperidine ring is the most prevalent *N*-heterocycle found in FDA-approved drugs (**Scheme 3.1**).



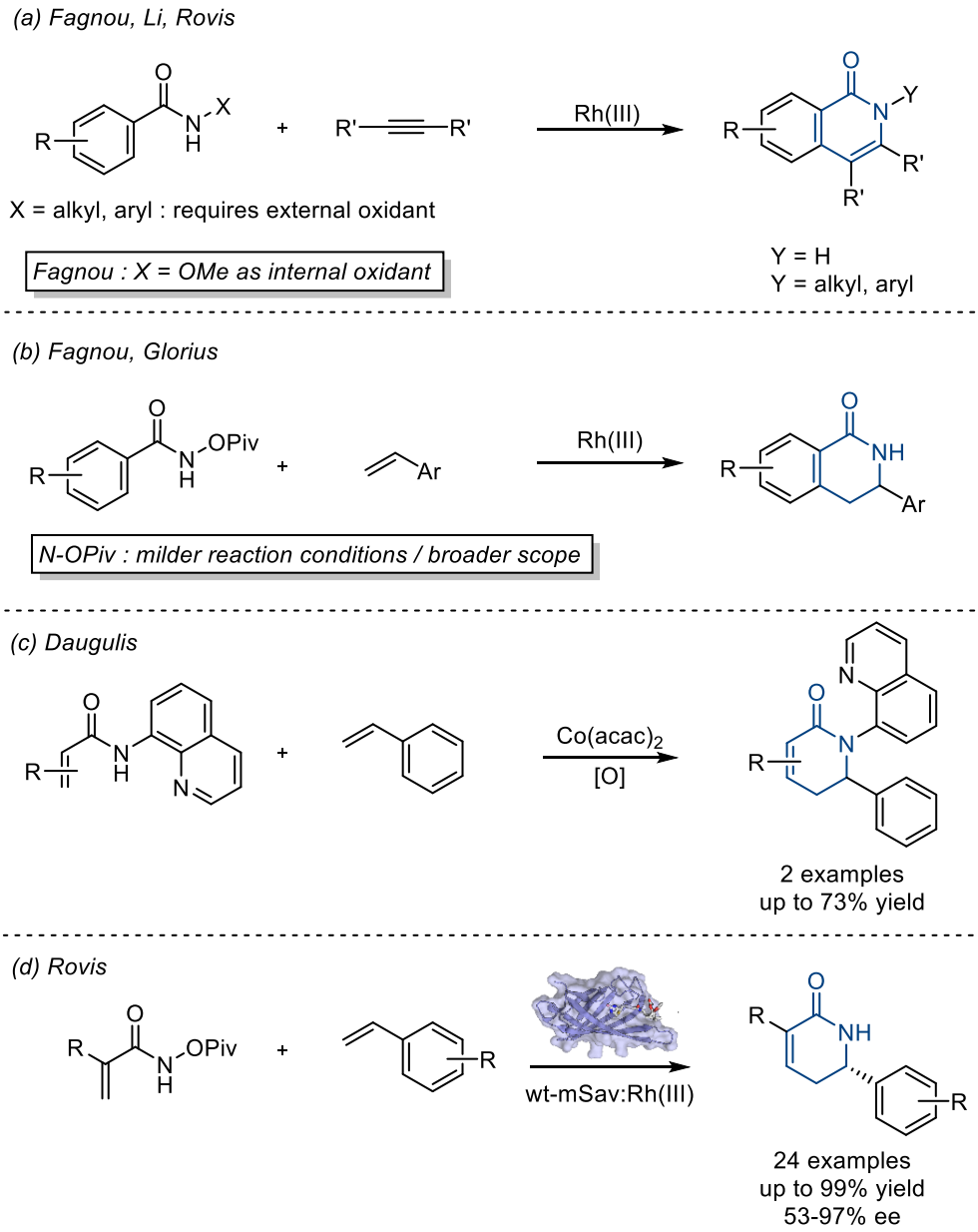
Scheme 3.1: Synthesis of piperidines.

Consequently, numerous synthetic methods have been developed for the synthesis of piperidines including both intra- and intermolecular pathways. Convergent synthetic strategies involving two different components have received great attention.[2-8] While these strategies are useful, they are often limited to specific classes of coupling partners and deliver products with a narrow range of substitution patterns. We envisioned direct access to α,β-unsaturated-δ-lactams from simple precursors would prove useful since they can be easily converted into piperidines through well-established reduction reactions.

In this context, Rh(III)-catalyzed C-H activation/annulation strategy has been utilized to synthesize related *N*-heterocycles (**Scheme 3.2**). Pioneering work by the groups of Fagnou,[9] Miura/Satoh,[10] Li,[11], and our group,[12] has demonstrated the directed C-H activation of benzamides with alkynes to yield isoquinolones (**Scheme 3.2a**). Significantly, the Fagnou group installed the *N*-OMe group as an oxidizing directing group that delivers unprotected isoquinolone products without an external oxidant. Later, Fagnou[13] and Glorius[14] groups introduced the *N*-acyloxy hydroxamate directing group, which allows alkene insertion to deliver dihydroisoquinolone (**Scheme 3.2b**).

The key to the success of the reaction with alkene was the discovery of the N-OPiv oxidizing directing group that resulted in milder reaction conditions and broader substrate scope. Later, the asymmetric variant of this process has been developed by Rovis/Ward using artificial metalloenzyme,[15] and Cramer with chiral Cp ligand.[16] However, related vinyl C-H activation is much less explored and only two examples of transition-metal-catalyzed vinyl C-H activation of acrylamides and the coupling with alkenes are documented. Specifically, the Daugulis group has utilized the aminoquinoline directing group in the presence of a Co catalyst and a stoichiometric amount of oxidant (**Scheme 3.2c**).[7] Recently, we reported asymmetric δ-lactam synthesis from *N*-

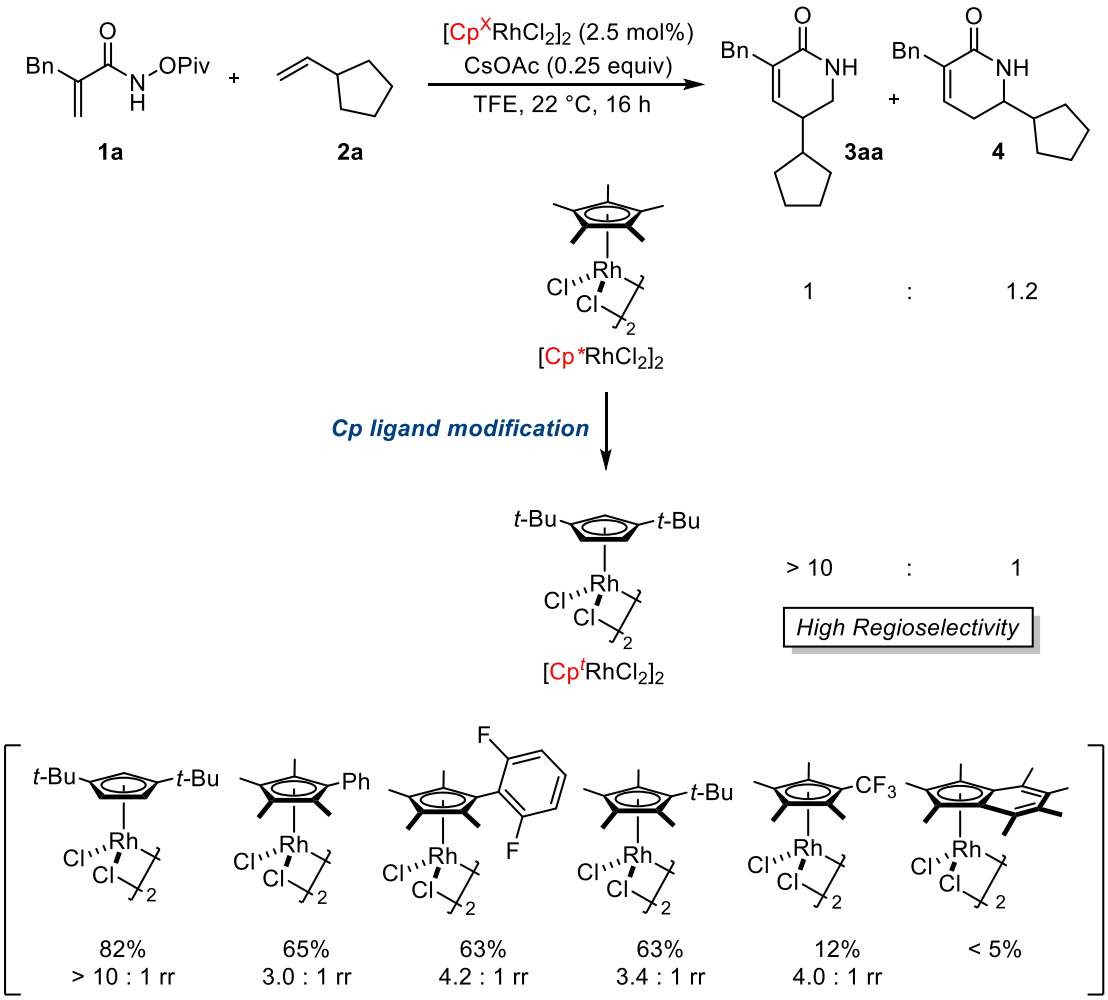
(pivaloyloxy)acrylamides using a monomeric streptavidin artificial metalloenzyme (**Scheme 3.2d**).[17] In both cases, only reactions with styrene-type alkenes are reported. For example, in our reaction with the artificial metalloenzyme, the reactions with unactivated alkenes such as cyclopentene and vinyl cyclohexane result in low yield and enantioselectivity.



Scheme 3.2: C-H activation and annulation strategy.

3.2 Reaction development

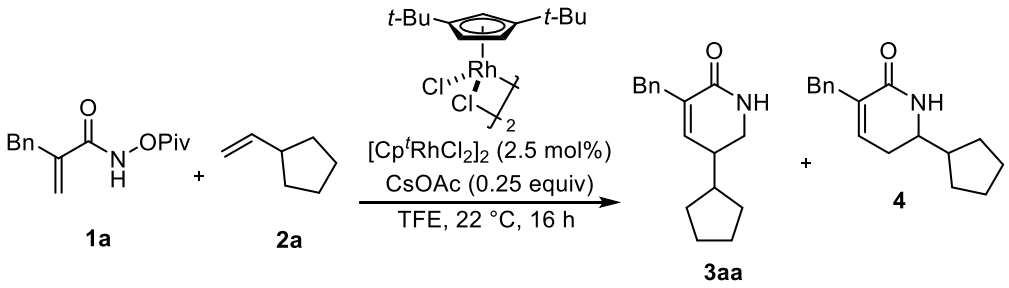
A former graduate student of the Rovis group, Dr. Natthawat Semakul, commenced the reaction development by examining the coupling of 2-benzyl-*N*-(pivaloyloxy)acrylamide (**1a**) and vinyl cyclopentane (**2a**) as model substrates. When he conducted the reaction in the presence of $[Cp^*RhCl_2]_2$ and CsOAc in trifluoroethanol (TFE), almost 1:1 regioselectivity was observed with moderate yield (**Scheme 3.3**).



Scheme 3.3: Improving regioselectivity with Cp ligand modification.

Inspired by previous work on the modification of Cp ligands on Rh(III) catalyst to improve regioselectivity,[18-24] we conducted a Cp ligand screen and found that the regioselectivity could be significantly improved with commercially available Cp^t ligand (Cp^t = 1,3-di-*tert*-butylcyclopentadienyl). After his graduation, I took over this project and continued to optimize the reaction conditions, explore the substrate scope, and investigate the reaction mechanism motivated by the relevance of the target δ-lactams, rapid access to the structure from readily available starting materials, and the potential to achieve diverse substitution patterns on piperidines.

For the reaction optimization, when $[Cp^*RhCl_2]_2$ is used as a catalyst, a nearly 1:1 mixture of regioisomers is formed in polar protic solvents (**Table 3.1**, entry 1–3).



entry	catalyst	solvent	yield of **3aa** (%)[a]	rr (**3aa**/**4**)[a]
1	$[Cp^*RhCl_2]_2$	MeOH	32	1 : 1.6
2	$[Cp^*RhCl_2]_2$	HFIP	34	1 : 1.1
3	$[Cp^*RhCl_2]_2$	TFE	38	1 : 1.1
4	$[Cp^tRhCl_2]_2$	MeOH	50	13.6 : 1
5	$[Cp^tRhCl_2]_2$	HFIP	54	8.7 : 1
6	$[Cp^tRhCl_2]_2$	TFE	**82**	10.2 : 1
7	$[Cp^*CoCl_2]_2$ or $[Cp^*IrCl_2]_2$	TFE	0	-

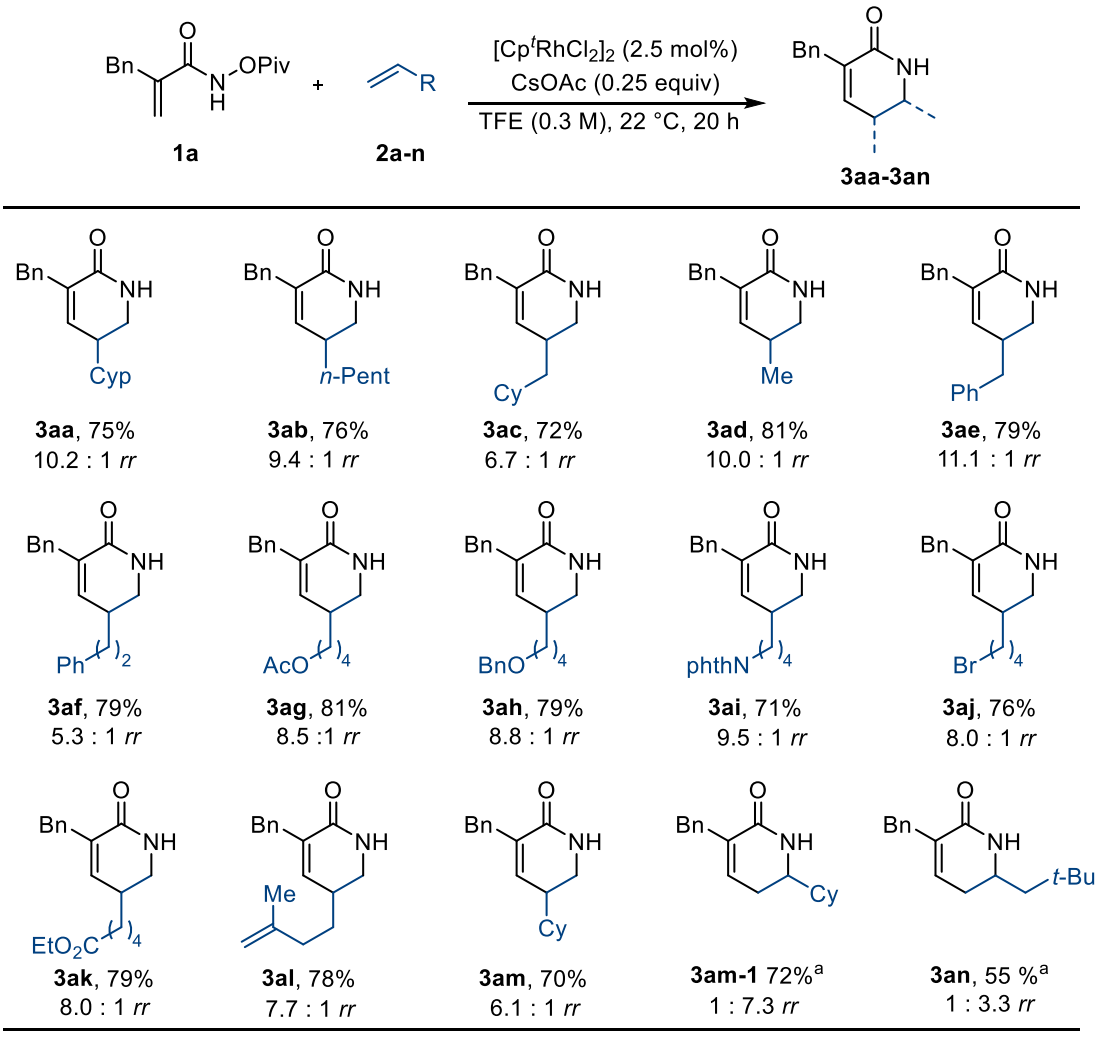
Reactions were conducted on a 0.1 mmol scale using **1a** (1.0 equiv) and **2a** (2.0 equiv).
[a]Determined by analysis of ^1H nuclear magnetic resonance (NMR) of the unpurified reaction mixture.

Table 3.1: Reaction optimization.

As mentioned above, the regioselectivity could be significantly improved with Cp^t ligand (entry 4–6). The regioisomers **3aa** and **4** are easily separable by column chromatography and the improved regioselectivity can be rationalized as a consequence of the steric repulsion between bulky Cp^t ligand and the substituent on the alkene coupling partner based on previous work with benzamides.[20-23] TFE was selected as a solvent for the optimized condition since it gives both good regioselectivity and good reaction yield compared to MeOH and HFIP. Other catalysts such as $[Cp^*CoCl_2]_2$ and $[Cp^*IrCl_2]_2$ fail to yield the desired product (entry 7). The reaction with styrene gives the opposite regioisomer (substituent close to new C-N bond) with both $[Cp^*RhCl_2]_2$ (64%, >15:1 dr) and $[Cp^tRhCl_2]_2$ (63%, >15:1 dr) catalysts.

3.3 Substrate scope

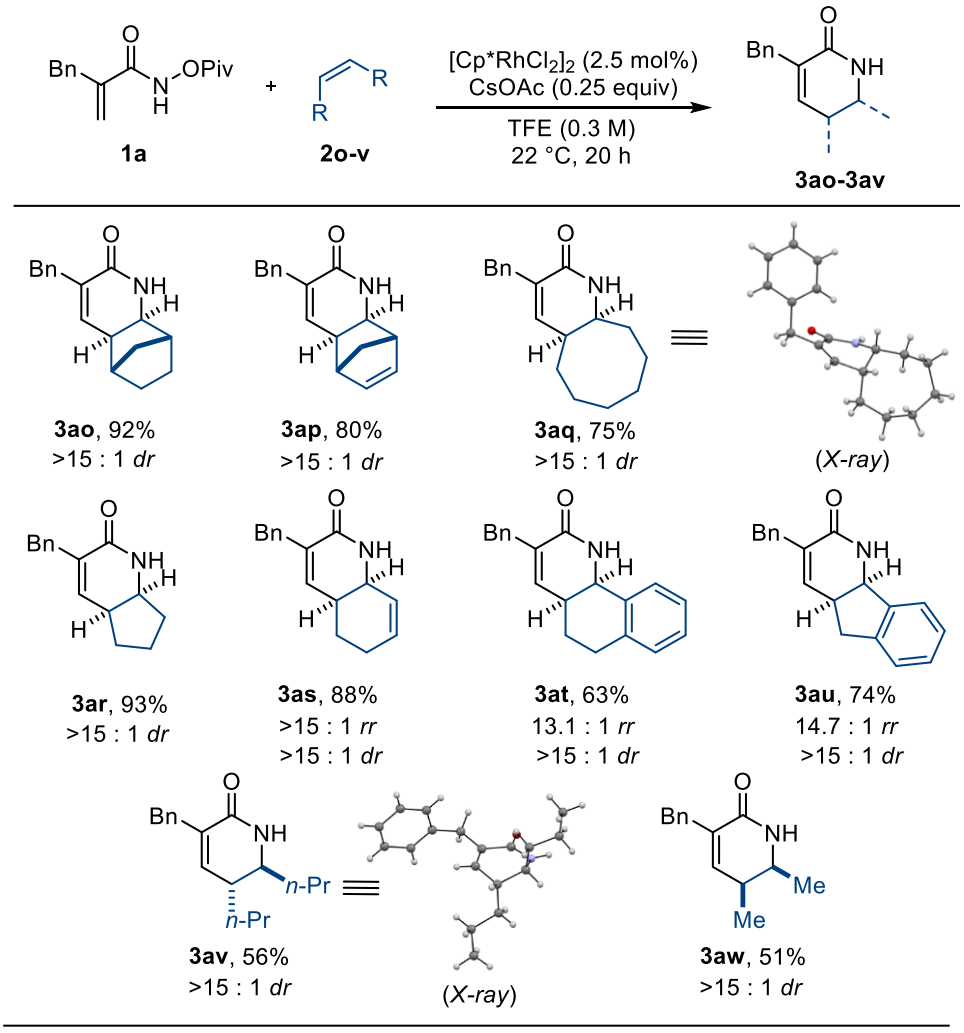
Having optimized the reaction conditions, we next explored the terminal alkene substrate scope using (**1a**) as an acrylamide coupling partner (**Scheme 3.4**). The reaction proceeds smoothly with terminal aliphatic alkenes such as 1-heptene (**2b**), allyl cyclohexane (**2c**), and gaseous propene (**2d**), giving the desired δ-lactam products in good yield and regioselectivity (**3aa**–**3ad**). A variety of functional groups such as phenyl, benzyl, protected alcohol or amine, bromide, and ester groups are all well tolerated (**3ae**–**3ak**). In the case of 2-methyl-1,5-hexadiene (**2l**), insertion occurs exclusively to give the mono-substituted terminal alkene over the gem-disubstituted alkene. Interestingly, vinyl cyclohexane (**2m**) and 4,4-dimethyl-1-pentene (**2n**) gave opposite regioisomers as the major product when $[Cp^*RhCl_2]_2$ was used as a catalyst. Next, the substrate scope with respect to internal alkenes was investigated (**Scheme 3.5**). For internal alkenes, $[Cp^*RhCl_2]_2$ was used as a catalyst instead of $[Cp^tRhCl_2]_2$ due to the lower yield observed with the latter catalyst.



[a][Cp*RhCl$_2$]$_2$ instead of [Cp^{t}RhCl$_2$]$_2$.

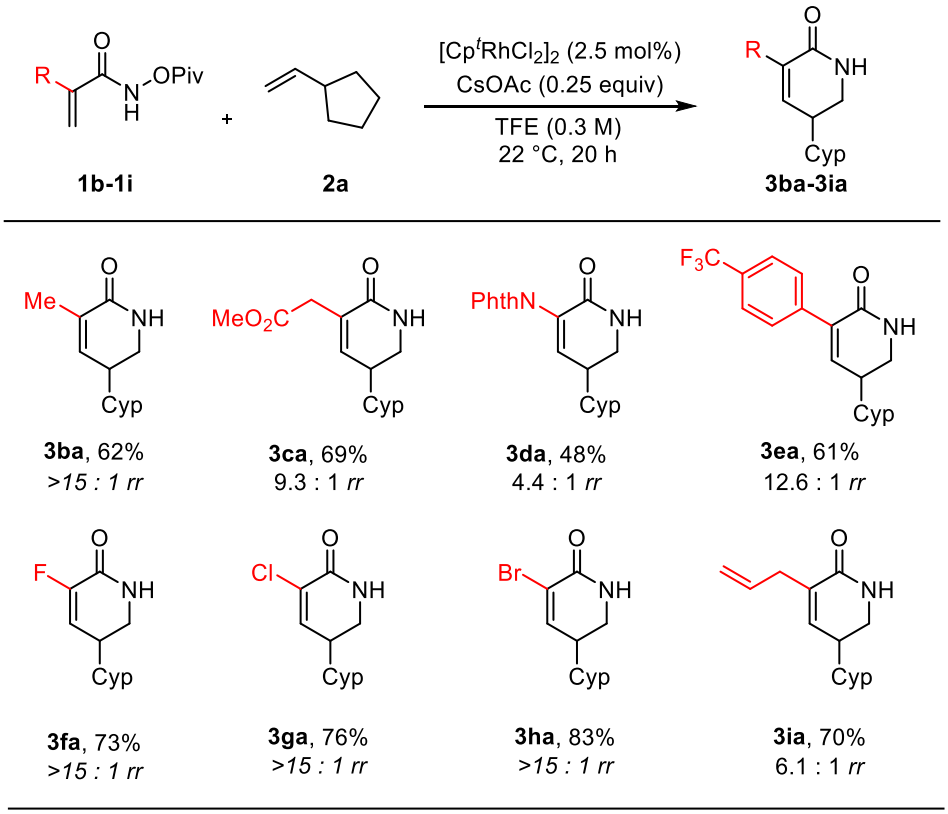
Scheme 3.4: Terminal alkene substrate scope.

Complex tricyclic structures are successfully constructed in a single step with excellent yields when norbornene (**2o**) and norbornadiene (**2p**) are used as coupling partners. [6,3,0] and [4.3.0] fused bicyclic δ-lactams are also formed with good yields when cis-cyclo-octene (**2q**) or cyclopentene (**2r**) are used. Surprisingly, cyclohexene does not lead to the desired product.



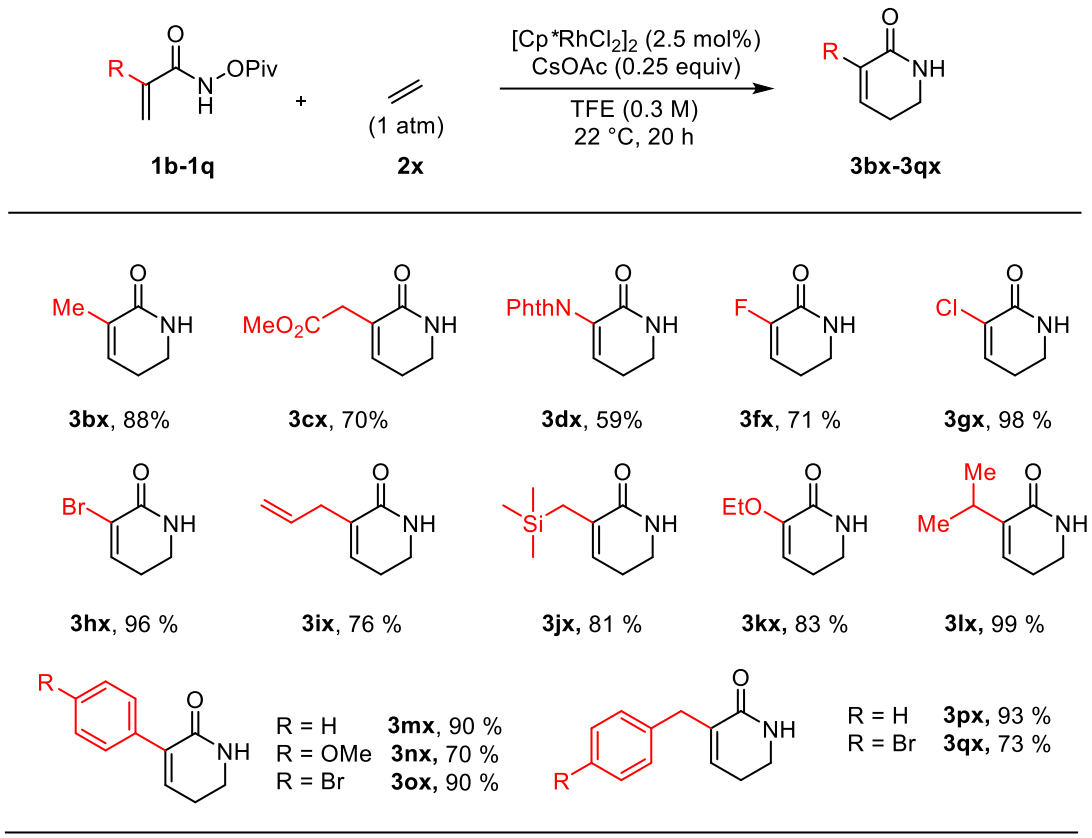
Scheme 3.5: Internal alkene substrate scope.

Excellent regioselectivity is observed for the reactions with cyclo-hexa-1,3-diene (**2s**), 1,2-dihydronaphthalene (**2t**), and 1*H*-indene (**2u**). Acyclic internal olefins containing cis or trans configurations, such as (*E*)-oct-4-ene (**2v**) and (*Z*)-but-2-ene (**2w**), also provide the desired product (**3av**, **3aw**) in good yield. All reactions with internal alkenes are highly diastereoselective and relative stereochemistry of **3aq** and **3av** were unambiguously determined by X-ray crystallography, which confirms retention of stereochemistry during the migratory insertion step.



Scheme 3.6: Acrylamide substrate scope.

Finally, we investigated the scope with respect to acrylamides using vinyl cyclopentane (**2a**) as a coupling partner (**Scheme 3.6**). *N*-(pivaloyloxy)acrylamides containing ester (**1c**), protected amine (**1d**), aryl (**1e**), and halide (**1f**–**1h**) groups delivered corresponding δ-lactam products with good yields and regioselectivities. 2-Methylene-*N*-(pivaloyloxy)-pent-4-enamide (**1i**), which contains two different terminal alkenes, gives δ-lactam exclusively, presumably due to the favored 5-membered rhodacycle formation after the C-H activation step. When 1 atm of ethylene (**2x**) is used as an alkene coupling partner of the reaction with acrylamides, the reactions give excellent yield with broad functional group tolerance (**Scheme 3.7**). This reaction could be used to synthesize mono-substituted piperidines through the reduction of a double bond and amide.

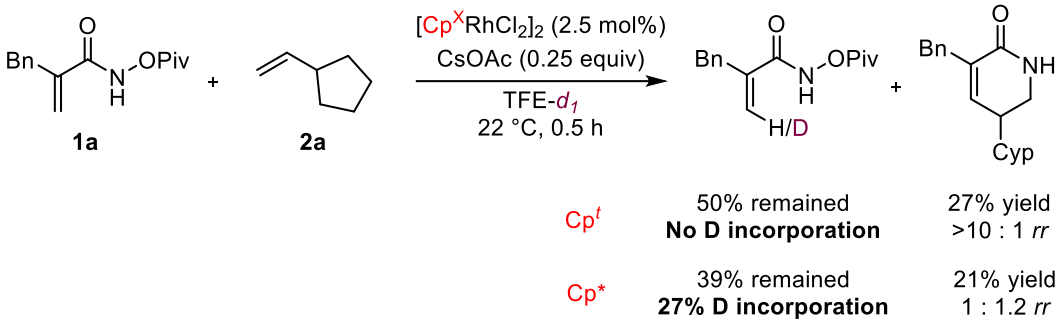


Scheme 3.7: Acrylamide substrate scope with ethylene.

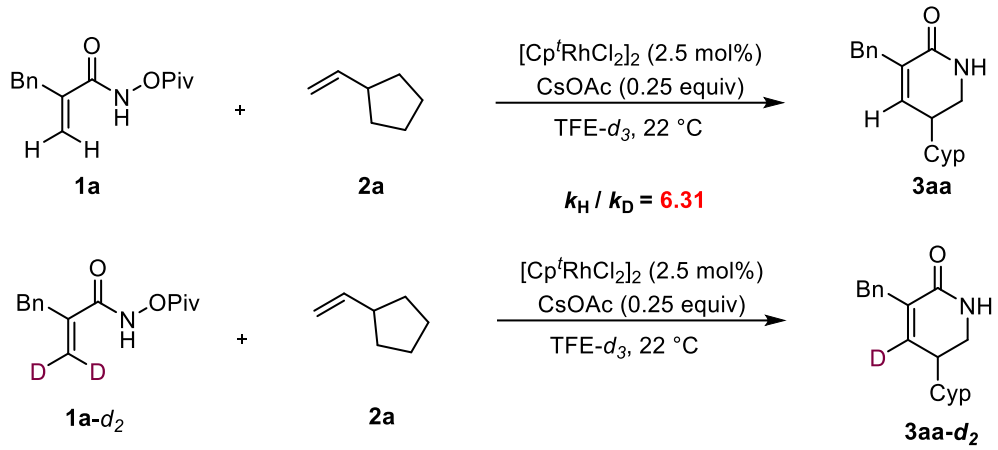
3.4 Mechanistic investigation

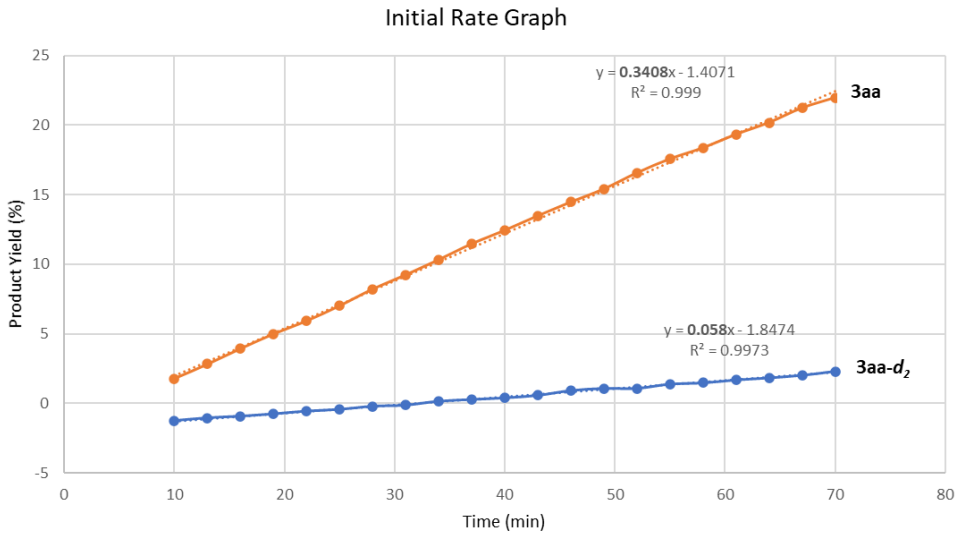
To obtain mechanistic insight, we first investigated the C-H activation step of the reaction (**Scheme 3.8a**). The reaction was conducted in TFE-d_1 and quenched when around 50% of the acrylamide substrate was consumed. Interestingly, the reversibility of the C-H activation depends on the Cp ligand on the Rh(III) catalyst. When $[Cp^tRhCl_2]_2$ was used as catalyst, deuterium incorporation was not observed in the unreacted acrylamide, which suggests C-H activation is

(a) Reversibility of C-H activation



(b) KIE determined from two parallel reactions



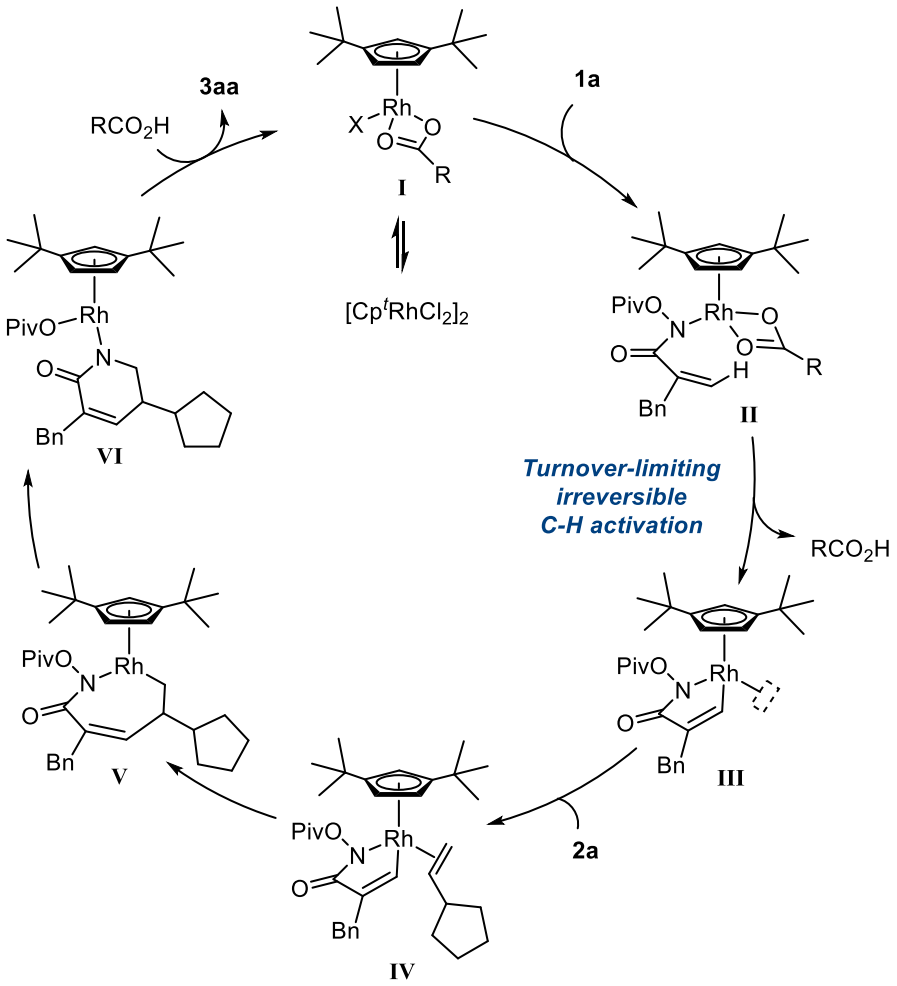


Scheme 3.8: Mechanistic investigation.

irreversible. In the case of $[Cp^*RhCl_2]_2$, the C-H activation is reversible, showing 27% deuterium incorporation on the recovered acrylamide. Next, the kinetic isotope effect (KIE) was measured from two separate reactions, one with a normal substrate containing a C-H bond and one with an analogous C-D bond (**Scheme 3.8b**).[25] The reaction was conducted in an NMR tube and the reaction progress was monitored *in situ* by ^{1}H NMR. The KIE value was calculated by comparing the initial reaction rate (slope) of each reaction. The observed primary KIE (k_H/k_D) value of 6.31 suggests that C-H bond cleavage occurs during the turnover limiting step. Overall, both experiments indicate that C-H activation is irreversible and the turnover-limiting step when Cp^tRh(III) is used as a catalyst.

3.5 Proposed mechanism

Based on previous work and our mechanistic investigation, we propose the following mechanism for the reaction (**Scheme 3.9**). First, coordination of the acrylamide substrate to active Rh(III) catalyst **I** generates intermediate **II**. At this stage, turnover-limiting irreversible C-H activation occurs to form 5-membered rhodacycle **III**. Subsequently, an alkene coupling partner coordinates and forms 7-membered rhodacycle **V** through regioselective migratory insertion. After C-N bond formation/N-O bond cleavage steps, intermediate **VI** releases the δ-lactam product with regeneration of the active Rh(III) catalyst **I**.

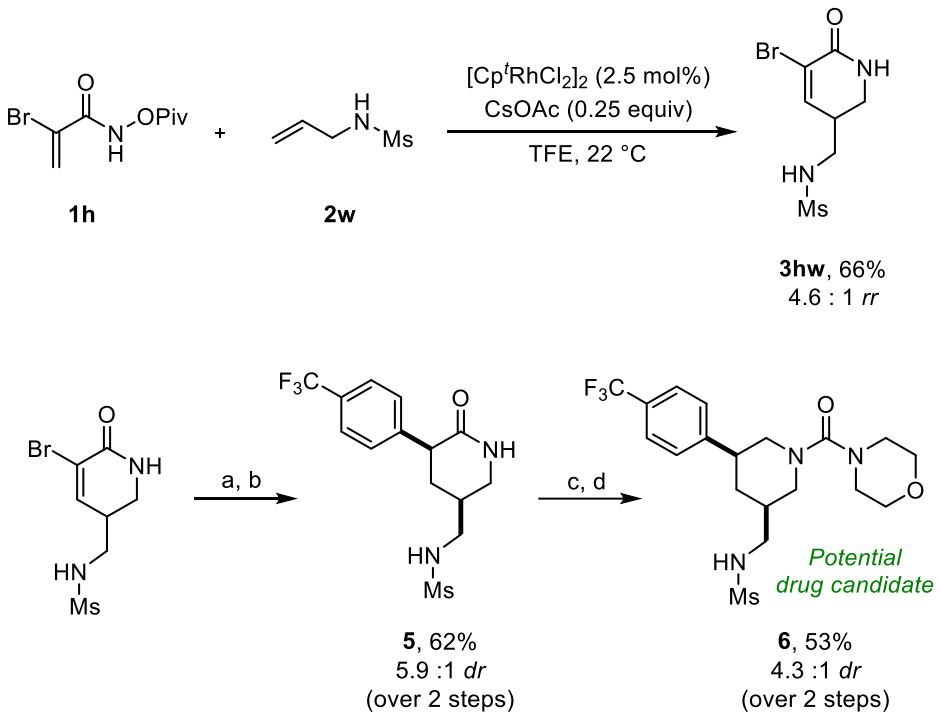


Scheme 3.9: Proposed mechanism.

3.6 Product derivatization

The utility of the developed method was demonstrated by the rapid synthesis of trisubstituted piperidine **6**, a potential drug candidate for cardiovascular disorders and tumors (**Scheme 3.10**).[26] The coupling reaction between 2-bromo-*N*-(pivaloyloxy)acrylamide (**1h**) and *N*-allylmethanesulfonamide (**2w**) gives the corresponding δ-lactam product (**3hw**) in a single step. The aryl moiety was installed through a Suzuki–Miyaura coupling reaction with 4-

(trifluoromethyl)-phenylboronic acid, and subsequent alkene hydrogenation resulted in compound **5**. After amide reduction and *N*-acylation, trisubstituted piperidine **6** was successfully prepared.



a) $PdCl_2(PPh_3)_2$ (10 mol%), 4-(trifluoromethyl)phenylboronic acid (3 equiv), dioxane/2 M Na_2CO_3 (0.06 M, 1:1), 60 °C, 1 h, 78%. b) Rh/C (10 wt%), H_2 (1 atm), MeOH (0.3 M), 22 °C, 4 h, 80%, 5.9:1 dr. c) BH_3·THF (5 equiv), THF, 60 °C, 3 h; 6 M HCl/MeOH, 60 °C, 3 h. d) Et_3N (1.5 equiv), morpholine-4-carbonyl chloride (1.2 equiv), 22 °C, 16 h. 53%, 4.3:1 dr (over 2 steps)

Scheme 3.10: Product derivatization.

3.7 Summary

In summary, we have developed a Rh(III)-catalyzed synthesis of α,β-unsaturated-δ-lactams from *N*-(pivaloyloxy)- acrylamides and unactivated alkenes. With this method, various δ-lactams containing a wide array of functional groups and complex bi/tricyclic structures were synthesized with good yield and regio/diastereoselectivity. Mechanistic investigation suggests

turnover-limiting irreversible C-H activation, subsequent regioselective migratory insertion, and C-N bond formation/N-O bond cleavage for the mechanism of the reaction.[27]

3.8 Reference

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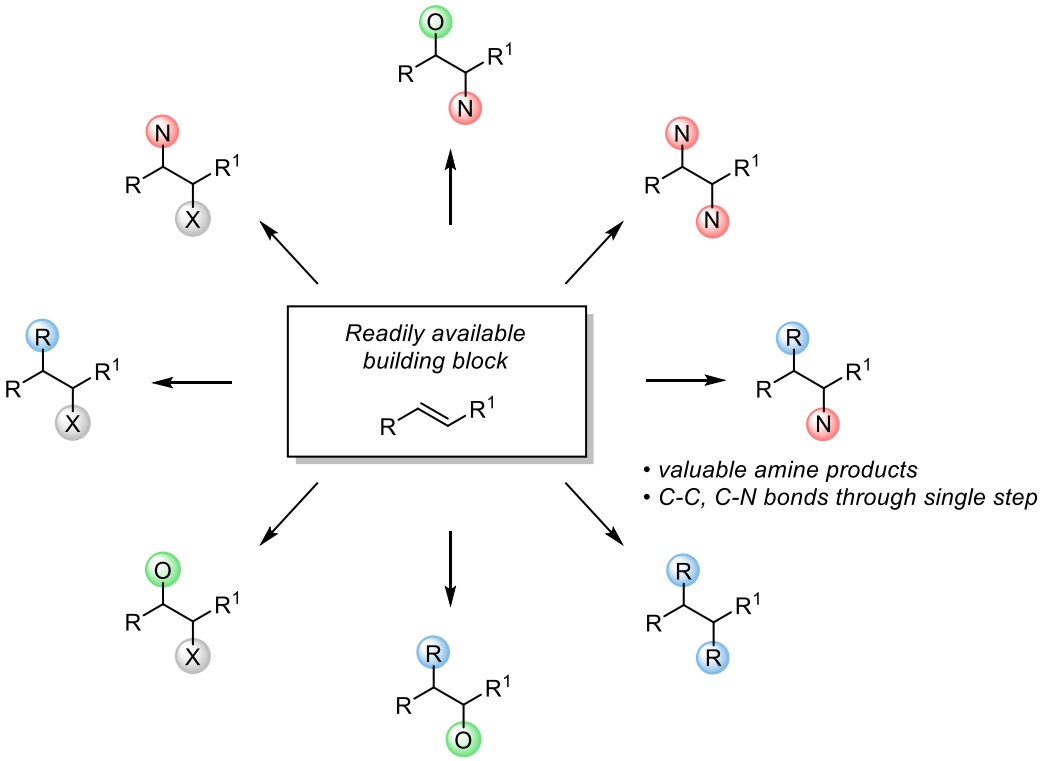
Chapter 4: Three-component *Syn*-Carboamination of Alkenes Using Arylboronic Acids and Dioxazolones

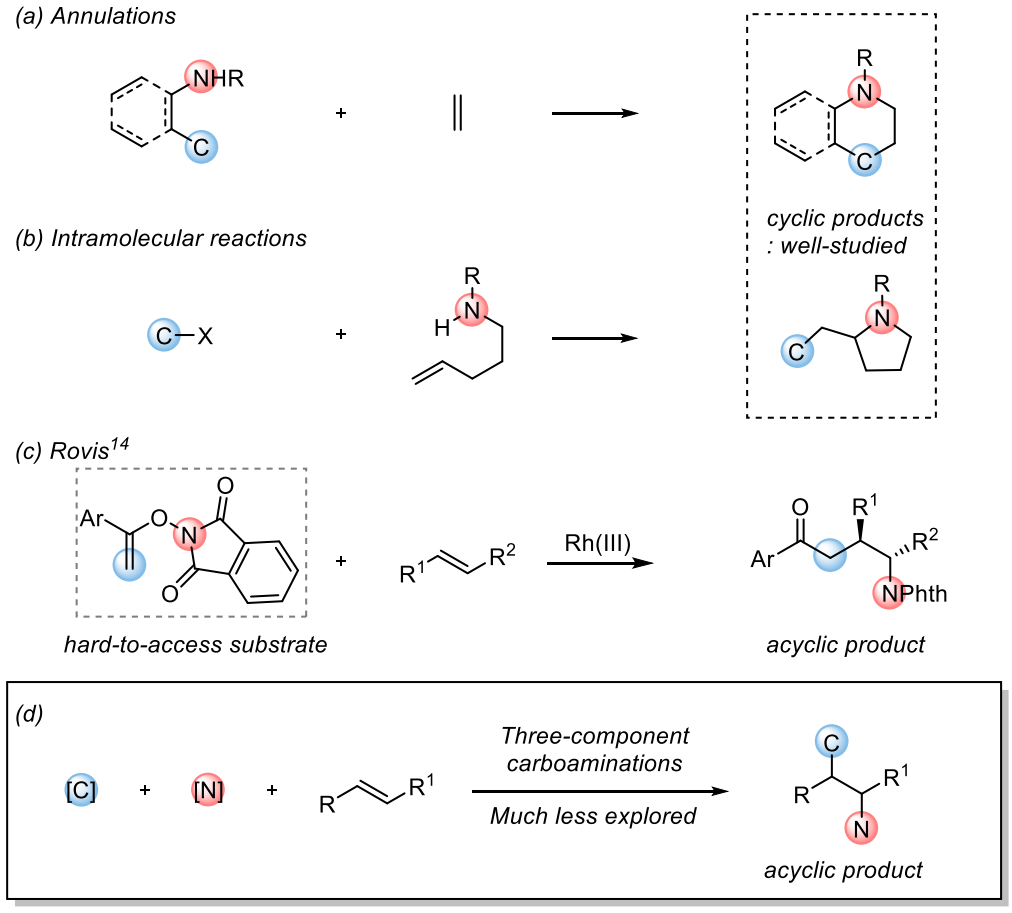
4.1 Introduction

Alkenes are ubiquitous functional groups in a myriad of organic compounds. Therefore the simultaneous installation of two functional groups across the alkene double bond in a stereoselective manner is one of the most powerful transformations in organic synthesis.[1-6] It provides an efficient way of rapidly increasing molecular complexity from readily available starting materials. Among various potential alkene difunctionalizations, the carboamination of alkenes offers direct access to valuable and pharmaceutically important amine products by forming both C-C and C-N bonds in a single step (**Scheme 4.1**).[7, 8]



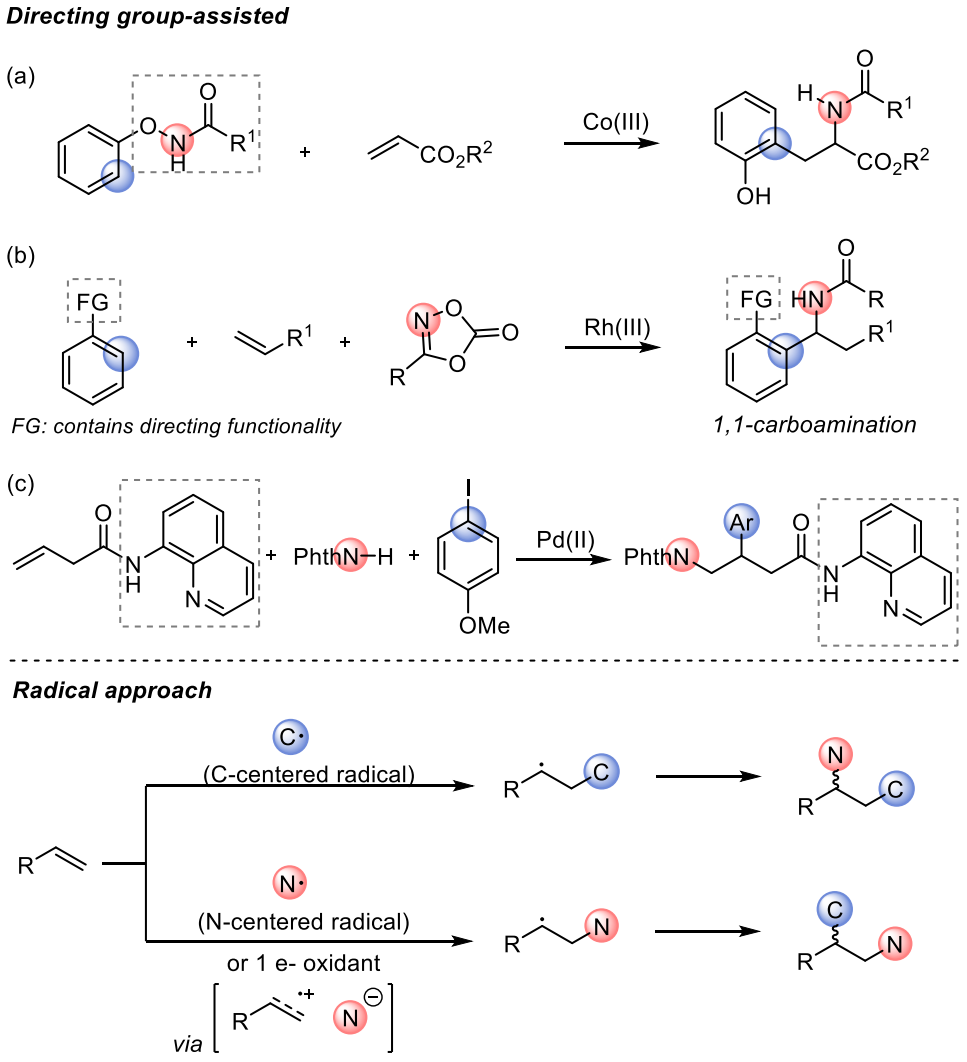
Scheme 4.1: Alkene difunctionalization.

A handful of powerful annulations[9, 10] or intramolecular carboaminations with tethered amine nucleophile[11-13] have been developed, which are currently limited to the synthesis of cyclic products (**Scheme 4.2**). Intermolecular carboamination of alkenes delivering acyclic amine products is relatively rare. In 2015, Rovis group described the first example of intermolecular, stereospecific, *syn*-carboamination of activated alkenes using *N*-enoxyphthalimide as both carbon and nitrogen source of the reaction to furnish acyclic amine products (**Scheme 4.2c**).[14] Since then, plenty of intermolecular carboamination papers have been reported and there are generally two approaches (**Scheme 4.3**).



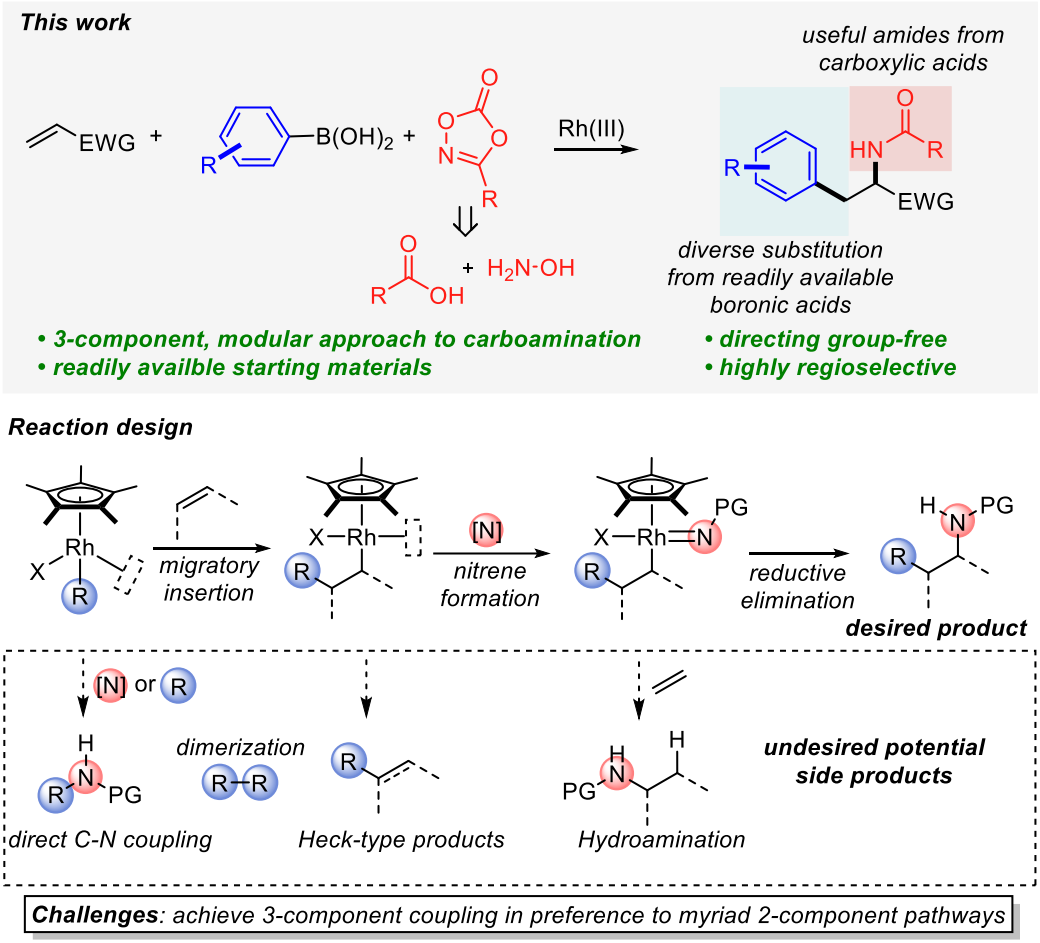
Scheme 4.2: Intermolecular carboamination of alkenes.

The first approach is directing group-assisted carboaminations. In 2016, Glorius group reported the carboamination of acrylates initiated by Cp*Co(III)-catalyzed C^{sp2}–H activation of *N*-phenoxyamides[15] followed more recently by Cramer's demonstration of an asymmetric version of this reaction (**Scheme 4.3a**).[16] *N*-phenoxyamide acts as an oxidizing directing group that enables selective *ortho* C-H activation of aryl ring and makes the overall process redox neutral. However, the necessity of directing functionality, and specific aryl substitution patterns (*ortho* hydroxyl group) of the carboamination products remain limitations.



Scheme 4.3: Approaches to intermolecular carboamination of alkenes.

Recently, Ellman reported the synthesis of an α-branched amine (**Scheme 4.3b**) through the Rh(III)-catalyzed three-component 1,1-carboamination of terminal alkenes that was also initiated by directing group assisted C-H activation.[17] Other significant contributions towards the linear carboamination of alkenes have been made utilizing Pd or Ni catalysis with olefins bearing covalently linked aminoquinoline directing groups (**Scheme 4.3c**).[18, 19] Alternative approaches to intermolecular carboamination is through single electron pathways involving nitrogen or carbon-centered radicals.[20-22]



Scheme 4.4: Rh(III)-catalyzed three-component carboamination.

Despite recent progress in the field, the current state-of-the-art in carboamination involves additional steps to install and remove the often undesired directing functionality, an inherent loss in stereocontrol imparted through open shell intermediates, or synthetically taxing substrates that limit the chemical space available to their practical application.

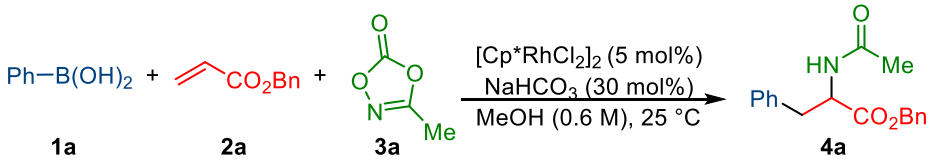
In searching for a more general solution to this problem, we became interested in developing an intermolecular 3-component carboamination that uses readily accessible carbon and nitrogen sources. Such a modular approach would enable the rapid synthesis of a diverse library of functionalized amine products by simply switching coupling partners (**Scheme 4.4**).

As a reaction design to achieve this goal, we envisioned that a carbon nucleophile coordinates to Cp*Rh(III) complex after transmetalation or ligand displacement then undergoes highly regioselective migratory insertion with activated alkenes in the absence of directing group. Subsequent reaction with nitrene precursors forms Rh-nitrene intermediates which will undergo reductive elimination to form a C-N bond and deliver desired carboamination products.

The challenge is that there are several undesired side product pathways as the reaction becomes a multi-component system. For example, after transmetalation, it can undergo dimerization of carbon source or direct C-N coupling if subsequent alkene migratory insertion is slow. Also, after migratory insertion of an alkene into a Rh-carbon bond, undesired β-hydride elimination or protodemetalation will result in Heck-type and hydroarylation products. Last, hydroamination side product also can be formed if the nitrogen source of the reaction directly reacts with the alkene coupling partner.

4.2 Reaction development

With this hypothesis in mind, we initiated a systematic investigation of carbon nucleophiles such as organoboron and organostannanes, with nitrene precursors such as azides, hydroxamates, and dioxazolones, under various reaction conditions. An initial hit was identified when we combined phenylboronic acid (**1a**), benzyl acrylate (**2a**), and 3-methyl-1,4,2-dioxazol-5-one (**3a**) with $[Cp^*RhCl_2]_2$ as a catalyst in methanol at room temperature delivering the desired carboamination product (**4a**) in 8% yield, with the mass balance comprised of Heck-type, hydroamination, and direct C-N coupling products. Inspired by a large library of commercially available boronic acids and readily accessible dioxazolones which can be easily prepared from carboxylic acids,[23] we decided to optimize the reaction and gratifyingly, achieved a 77% yield of the desired carboamination product (**4a**) (Table 1, entry 1, see Appendix C for details).



1a **2a** **3a** **4a**

entry	deviation from standard conditions	yield of **4a**[a] (%)
1	None	77 (68)[b]
2	Other nitrene precursors instead of **3a**	-
3	$[Cp^*Rh(MeCN)_3](SbF_6)_2$ instead of $[Cp^*RhCl_2]_2$	-
4	$[Rh(COD)_2Cl]_2$ instead of $[Cp^*RhCl_2]_2$	-
5	NaOAc instead of $NaHCO_3$	5
6	60 °C instead of 25 °C	42
7	**1a** (2 equiv)/ **2a** (1 equiv)/ **3a** (1 equiv)	64
8	1 mmol scale with 2.5 mol% $[Cp^*RhCl_2]_2$	78 (69)[b]

Reactions were conducted on a 0.1 mmol scale using **1a** (2.5 equiv), **2a** (3.0 equiv), and **3a** (1 equiv). [a]Determined by analysis of ^{1}H NMR of the unpurified reaction mixture. [b]Isolated yield.

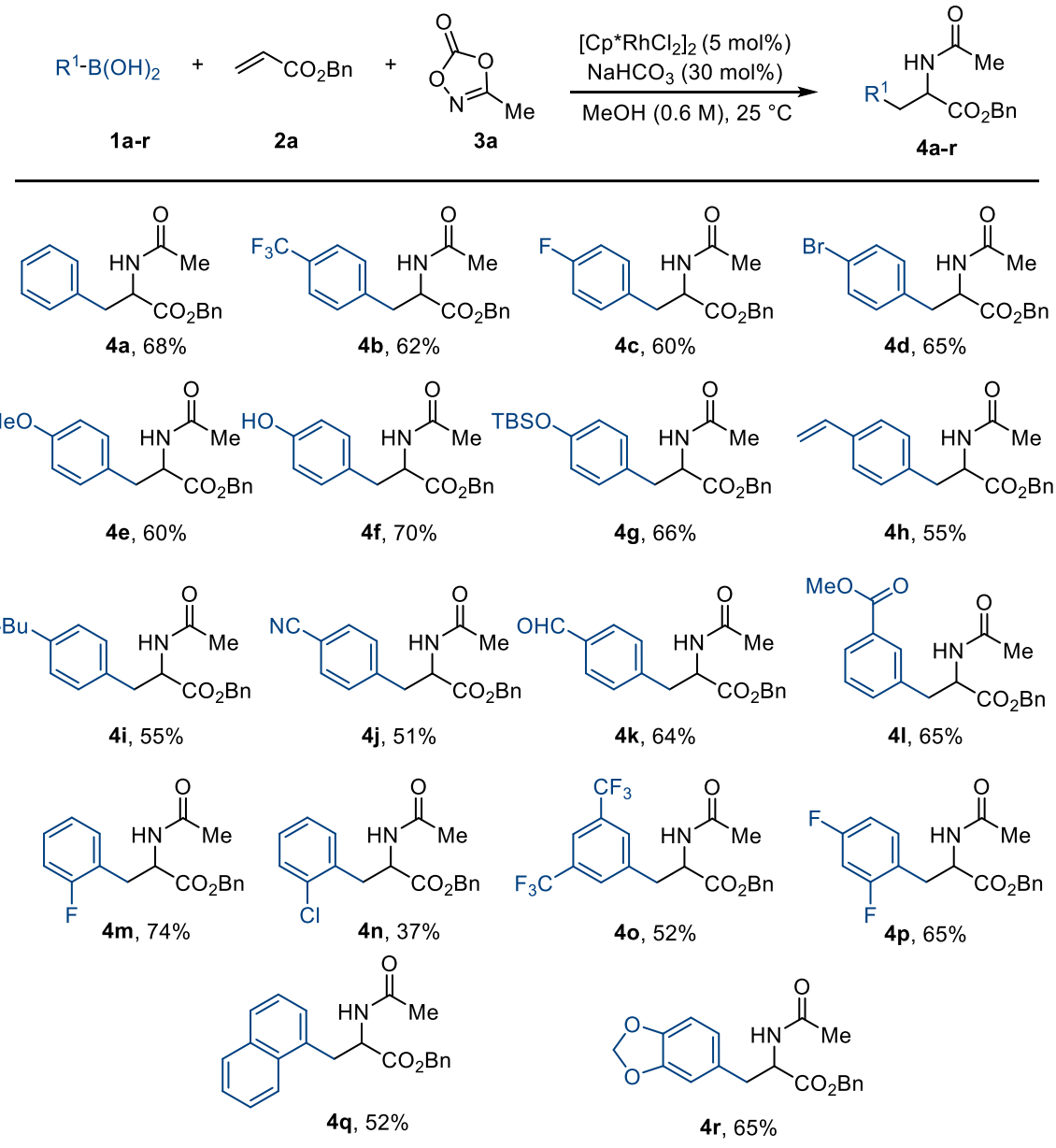
Table 4.1: Reaction optimization.

Other nitrene precursors[10, 24-26] that are frequently used for amination chemistry with Cp* group 9 catalysis are completely ineffective for this chemistry. In the cases of Ts-N_3, Ts-NH-OPiv, 5,5-dimethyl-1,4,2-dioxazole, and 1,4,2-dioxazol-5-thione, no conversion of starting materials is observed. When *N*-(pivaloyloxy)amides are used as nitrogen source of the reaction, direct C-N coupling product was observed as a major side product and *N*-(tetrafluorophenoxy)amides give Heck-type and hydroarylation side products in high yield. (entry 2, see Appendix C for details).

Also, the choice of the catalyst is important since cationic Rh(III) catalysts, such as $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (entry 3) or an *in situ* generated cationic Rh(III) complex, do not lead to the desired product. Several Rh(I) catalysts such as $[Rh(COD)_2Cl]_2$ (entry 4) that are commonly used for conjugate addition chemistry with arylboronic acids,[27-29] or other Cp* group 9 catalysts such as $[Cp^*CoCl_2]_2$ or $[Cp^*IrCl_2]_2$, failed to deliver the carboamination products. Screening of base additives shows that bicarbonate, carbonate, or fluoride generally gives a higher reaction yield compared to acetates, and $NaHCO_3$ was selected as the optimal additive. When acetates are used as an additive, the reaction yield is significantly decreased and the Heck-type product becomes a major product of the reaction in low yield. One possible explanation is that acetates act as a bidentate ligand and prevent the coordination of dioxazolone (entry 5).

The reaction proceeds smoothly at room temperature and tends to give a lower yield at a higher temperature, as shown with the 42% yield obtained when the reaction was conducted at 60 °C (entry 6). When both alkene (**2a**) and dioxazolone (**3a**) are used as the limiting reagent of the reaction, the reaction gives a synthetically useful 64% yield (entry 7), and a 77% yield was achieved when **1a** (2.5 equiv), **2a** (3 equiv), and **3a** (1 equiv) were used for the reaction (See Appendix C for details). Lastly, the reaction can be performed on a 1.0 mmol scale with 2.5 mol% catalyst loading without loss of the product yield (entry 8).

4.3 Reaction scope

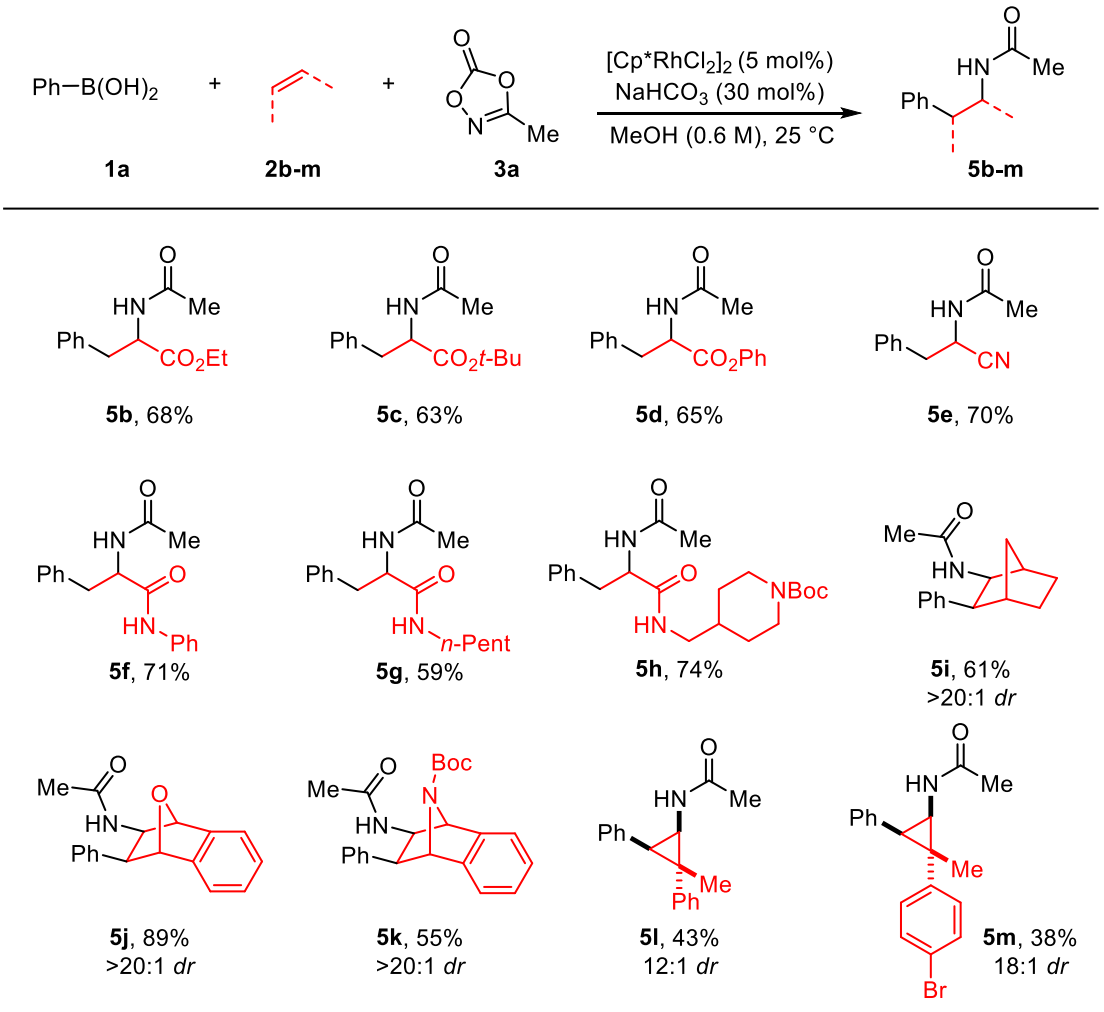


Scheme 4.5: Boronic acid substrate scope.

Having optimized the reaction conditions, we next sought to explore the scope of the transformation. The reaction with aryl boronic acids containing a variety of functional groups at the para position of phenyl ring proceeds smoothly, delivering products with -CF_3 (**4b**), -F (**4c**), -Br (**4d**), -OMe (**4e**), hydroxy (**4f**), silyl ether (**4g**), alkene (**4h**), alkyl (**4i**), nitrile (**4j**), and aldehyde

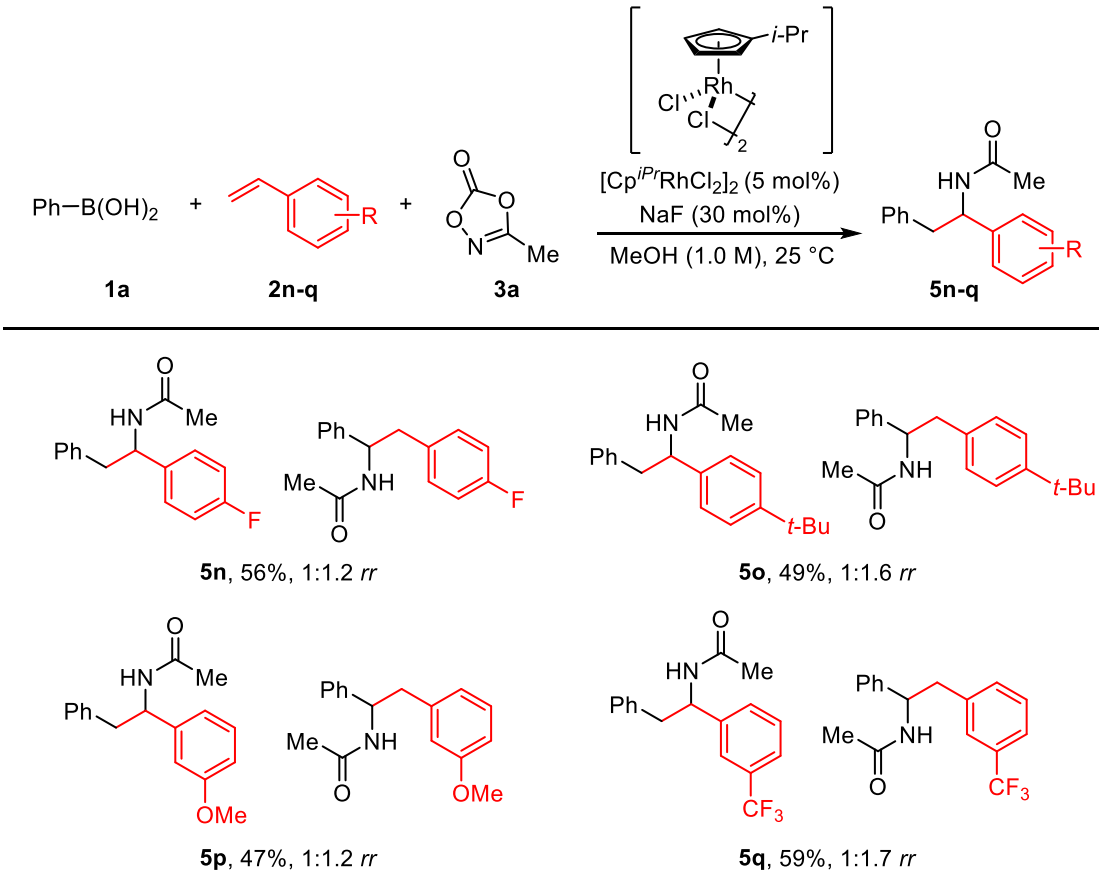
(**4k**) functional groups in good yield (**Scheme 4.5**). Aryl boronic acids with a substituent in the meta position (**4l**), having multiple substituents (**4o**, **4p**), naphthyl boronic acid (**4q**), and 3,4-methylenedioxyphenylboronic acid (**4r**) also work well in this reaction. In the case of vinyl boronic acids (such as 1-penten-1-ylboronic acid) or alkyl boronic acids the reactions are unsuccessful. (see Appendix C for limitations).

For alkene substrate scope, the reaction with monosubstituted acrylates gives corresponding phenylalanine derivatives (**5b**-**5d**) in good yield (**Scheme 4.6**).



Scheme 4.6: Alkene substrate scope.

Acrylonitrile (**2e**) also works well in this reaction, providing a potential for further functional group derivatization. Secondary acrylamides are also good alkene coupling partners, delivering carboamination products (**5f-5h**) containing two amide bonds. The reaction with bridged bicyclic alkenes such as norbornene (**2i**), oxabenzonorbornadiene (**2j**), and aza-benzonorbornadiene (**2k**) gives *syn*-carboamination products (**5i-5k**) in good yield and excellent diastereoselectivity. In the case of the reactions with cyclopropenes (**2l-2m**), the reaction occurs cis to the methyl group, presumably because of a smaller steric demand during the alkene migratory insertion step, giving cyclopropyl amine products (**5l-5m**) in high diastereoselectivity.

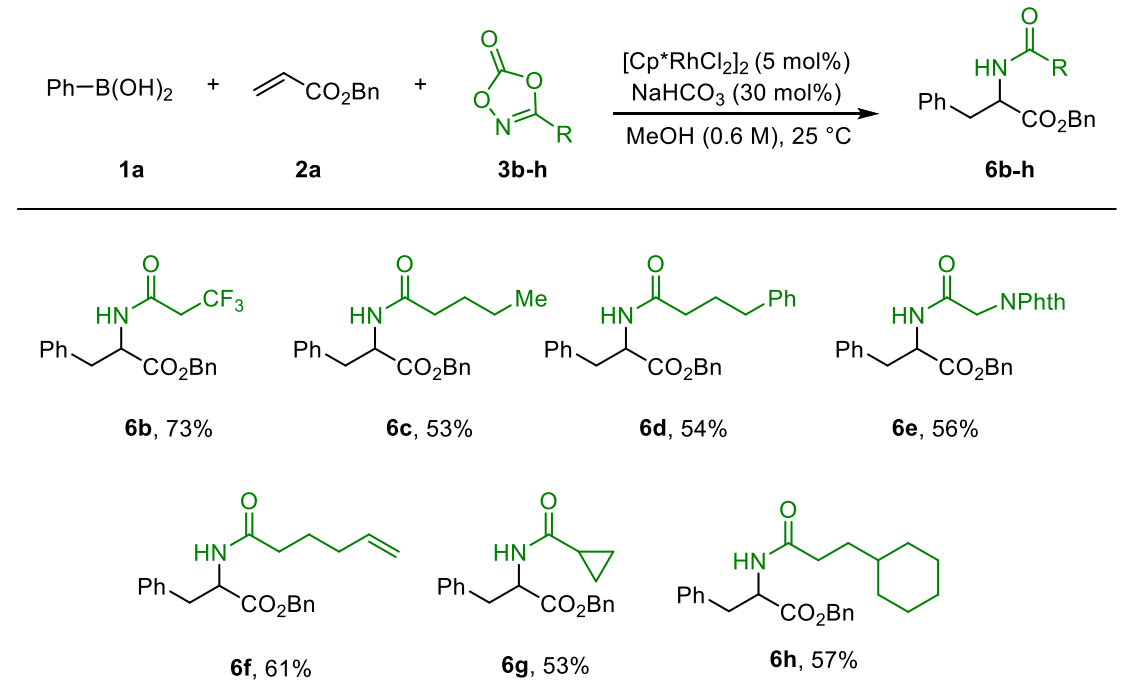


1a (2 equiv), **2** (1 equiv), **3a** (5 equiv) were used.

Scheme 4.7: Styrene scope.

Internal alkenes such as ethyl crotonate, ethyl cinnamate, cyclopentenone, or styrene do not lead to the product formation and direct *N*-phenylation products are observed as a major side product of the reaction, presumably due to a slow alkene migratory insertion (see Appendix C for details). In the case of the reaction with styrene (**Scheme 4.7**), the overall yield for the carboamination can be improved by using an electron-deficient $Cp^{iPr}Rh(III)$ catalyst with an access amount of dioxazolones. However, a mixture of two regioisomers (1,1- and 1,2-carboamination) is observed with low selectivity. We believe this system accelerates the alkene migratory insertion step with styrenes, but β-hydride elimination/Rh-hydride re-insertion occurs before Rh-nitrene formation to give a mixture of regioisomers.

Lastly, a variety of functional groups can be installed at the amide side chain using dioxazolones with different substituents at the 3 positions (**3b**-**3h**) prepared from corresponding carboxylic acids (**Scheme 4.8**).



Scheme 4.8: Dioxazolone substrate scope.

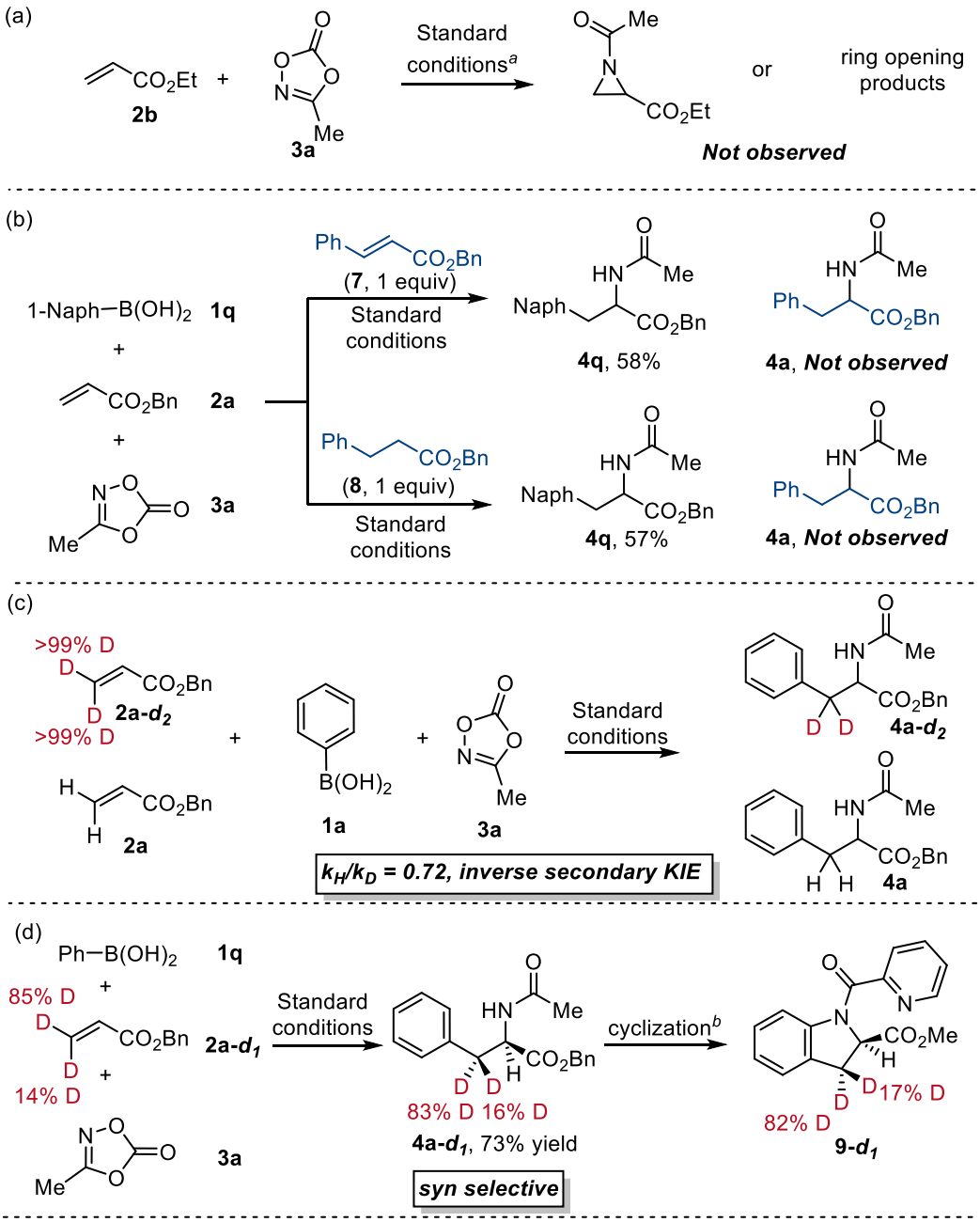
The reactions with dioxazolone **3d** or **3f** containing allylic or benzylic C-H bonds give the carboamination products selectively (**6d**, **6f**). These are noteworthy as they have been used for intramolecular C-H amination chemistry.[30] The carboamination occurs intermolecularly in preference to an intramolecular C-H insertion suggesting a mechanistic dichotomy with Chang's Ir-based system.

4.4 Mechanistic investigation

We next designed a series of experiments to interrogate the mechanism of the reaction. First, we conducted the reaction under standard conditions, but without phenylboronic acid (**Scheme 4.9a**). As a result, neither *N*-acyl aziridine nor aziridine ring-opening products[26] is observed after the reaction. This strongly indicates that the Rh(III)-catalyzed alkene aziridination and subsequent ring-opening with phenylboronic acid is unlikely as the mechanism of the reaction.

During the optimization study, we observed Heck-type (**7**) and hydroarylation products (**8**) as side products of the reaction, presumably formed through β-hydride elimination and proto-demetallation after the alkene migratory insertion (**Scheme 4.10**). To determine whether these side products give the desired carboamination product (**4**), we separately synthesized both benzyl cinnamate (**7**) and benzyl 3-phenylpropanoate (**8**) and they were subjected to the reaction using 1-naphthyl boronic acid (**2q**) as the carbon source of the reaction (**Scheme 4.9b**). While both reactions give the desired product (**4q**) from 1-naphthyl boronic acid (**2q**) in good yield, carboamination products (**4a**) from these side products (**7** or **8**) are not observed. These experiments suggest **7** and **8** are off-cycle side products that do not re-enter the catalytic cycle. In addition, monitoring the reaction progress with ^{1}H NMR indicates that the reaction with

dioxazolone that leads to product formation is faster than β-hydride elimination at the beginning of the reaction. The amount of β-hydride elimination product increases after consumption of limiting dioxazolone (**3a**) (see Appendix C for the details).



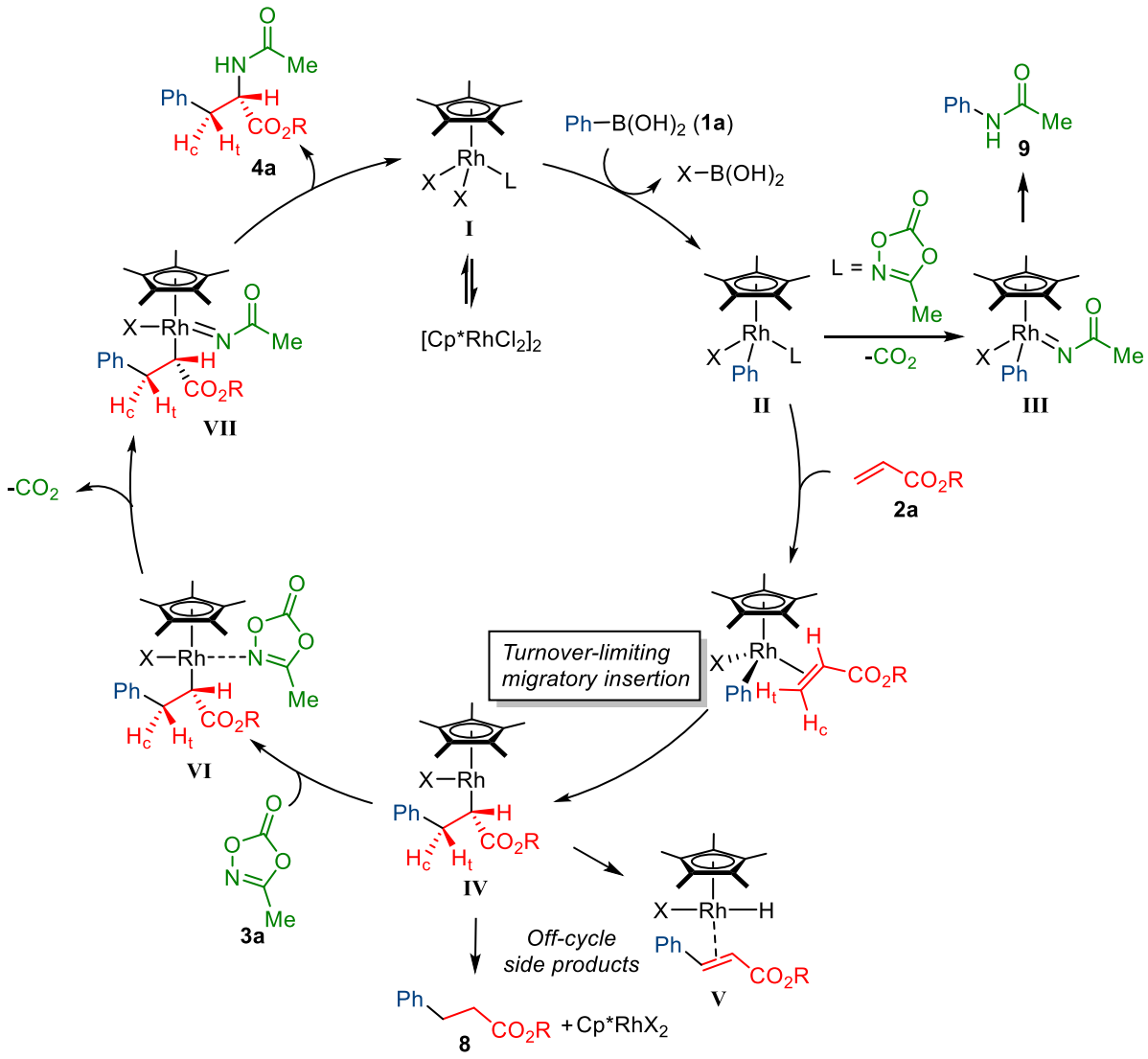
Scheme 4.9: Mechanistic investigation.

In order to determine the turnover limiting step of the reaction, we investigated the alkene migratory insertion step with benzyl acrylate (**2a**) and deuterated benzyl acrylate (**2a-*d*$_2$**). The inverse secondary kinetic isotope effect (KIE) value of 0.72 measured from the intermolecular competition experiment (**Scheme 4.9c**) or 0.55 calculated by comparing the initial rate of two separate reactions, one with benzyl acrylate (**2a**) and one with deuterated benzyl acrylate (**2a-*d*$_2$**) (see Appendix C for details) suggest sp^2 to sp^3 hybridization change occurs during the turnover limiting step of the reaction.[31, 32]

In order to determine the relative stereochemistry of the product, we conducted the reaction with mono-deuterated benzyl acrylate (**2a-*d*$_1$**, 85:14 E/Z) (**Scheme 4.9d**). Interestingly, the reaction gives the product (**4a-*d*$_1$**) containing almost identical deuterium incorporation with starting alkene (**2a-*d*$_1$**) which suggests the carboamination is highly diastereoselective. The product was cyclized by Pd-catalyzed intramolecular C-H amidation,[33] which confirmed *syn*-carboamination of the alkene.

4.5 Proposed mechanism

Based on these experiments, we propose the following mechanism for the reaction (**Scheme 4.10**). First, the active monomeric Rh complex **I** undergoes transmetalation with phenylboronic acid (**1a**) to give Rh-phenyl complex **II**. Next, turnover limiting migratory insertion into the Rh-aryl bond forms Rh(III) intermediate **IV**. Subsequently, dioxazolone (**3a**) coordinates to the electron-rich alkyl Rh(III) complex (I**V**) followed by Rh-nitrene formation with the exclusion of CO_2. The desired *syn*-carboamination product (**4a**) is formed after reductive elimination and proto-demetallation with the regeneration of active Rh catalyst **I**.

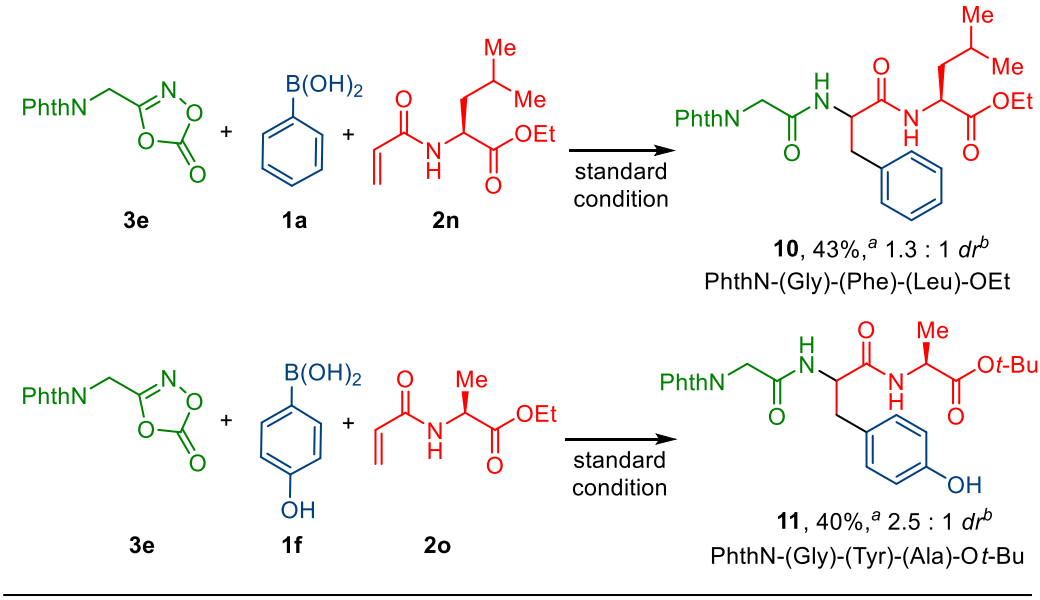


Scheme 4.10: Proposed mechanism.

4.6 Application to peptide synthesis

As a potential application of the newly developed methodology, we synthesized peptide chains using dioxazolones and alkenes prepared from natural amino acids (**Scheme 4.11**). The

reaction with glycine-derived dioxazolone (**3e**), alkene (**2n**) synthesized from L-leucine, and phenylboronic acid (**1a**) delivers tripeptide, PhthN-(Gly)-(Phe)-(Leu)-OEt (**10**) in 43% yield albeit low diastereoselectivity. Using 4-hydroxyphenylboronic acid (**1f**), tyrosine residue was successfully formed to synthesize PhthN-(Gly)-(Tyr)-(Ala)-Ot-Bu (**11**). Currently, a 2nd-year graduate student of the lab, Chris Lamartina, is trying to improve the reaction yield and diastereoselectivity to achieve a diastereoselective synthesis of longer and general peptide chains by forming nonnatural phenylalanine residue with a choice of easily available boronic acids.



Reactions were conducted on a 0.1 mmol scale. [a]Isolated yield. [b]Determined by analysis of ^{1}H NMR of the purified product.

Scheme 4.11: Application to peptide synthesis.

4.7 Summary

In summary, we have developed Rh(III)-catalyzed 3-component regioselective *syn*-carboamination of alkenes. The reaction shows a broad scope with a variety of commercially

available arylboronic acids and dioxazolones easily prepared from carboxylic acids. Mechanistic investigations suggest alkene migratory insertion to be the turnover limiting step supported by secondary KIE. In addition, deuterium labeling experiments provide experimental evidence for stereoselective *syn*-carboamination process. This method provides a rapid access to valuable amines including non-natural α-amino acids from abundant alkenes with excellent regioselectivity and high diastereoselectivity with internal cyclic alkenes.

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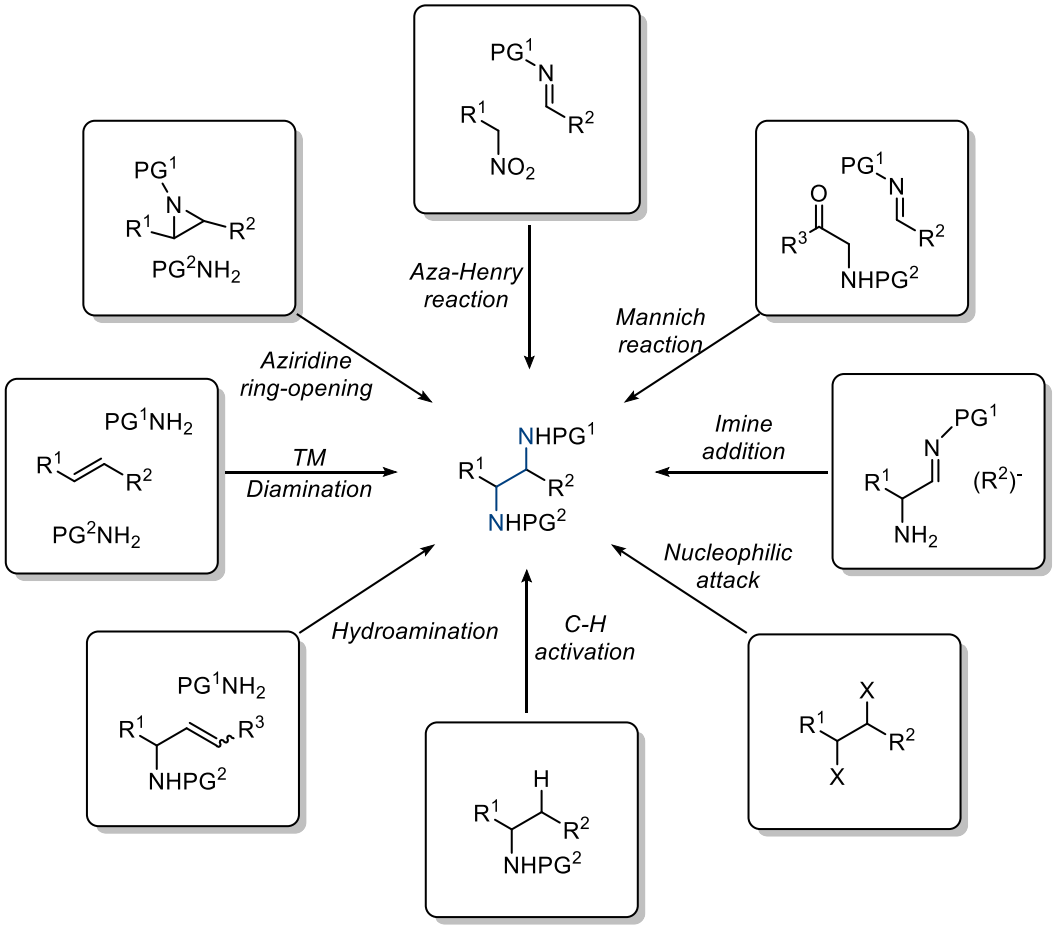
Chapter 5: Three-component Diamination of Unactivated Alkenes

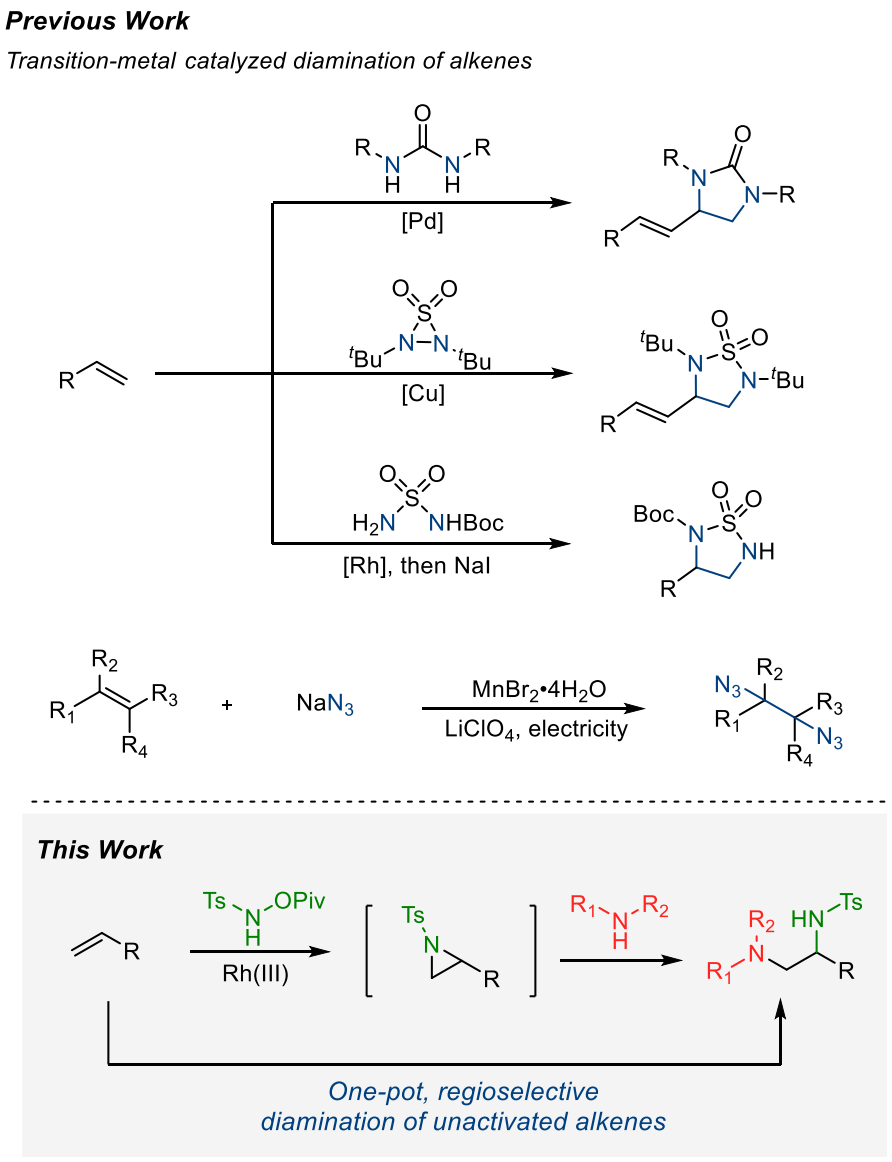
5.1 Introduction

The 1,2-vicinal diamine is a prevalent structural motif in natural products and pharmaceuticals. Moreover, they are commonly utilized as ligands on various metal complexes that catalyze essential organic transformations.[1-3] Owing to the high demand, the development of efficient synthetic strategies for the synthesis of 1,2-diamines has been actively pursued (**Scheme 5.1**).[2, 4] Several notable synthetic approaches exist including aza-Henry reaction,[5-7] Mannich reaction between α-amino-compounds and imines,[8, 9] and the addition of nucleophile onto α-amino imines.[10]



Scheme 5.1: Synthesis of vicinal diamines.

Among the potential synthetic precursors for the synthesis of vicinal amines, alkenes are ideal – they are ubiquitous feedstock materials, and unreactive enough to the other transformations. Thus, the simultaneous addition of two nitrogen functionalities to the alkene double bond is a straightforward and useful way to access 1,2-vicinal diamines (**Scheme 5.2**).



Scheme 5.2: Transition metal-catalyzed alkene diaminations.

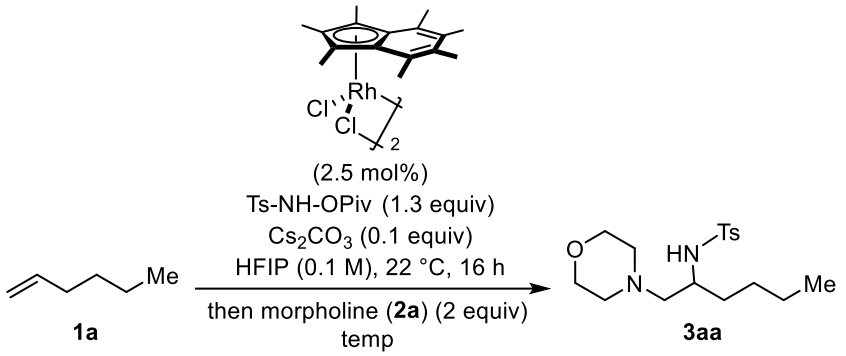
However, aside from some prominent successes (**Scheme 5.2**),[11-19] transition-metal-catalyzed 1,2-diamination of alkenes is significantly underdeveloped compared to the much better-established dihydroxylation and aminohydroxylation of alkenes. Presumably, this is because 1,2-diamines are generally good ligands and can act as a chelating ligand for the metal complex.

Alternatively, the nucleophilic ring-opening of aziridines by amines is an efficient strategy to access diamines from readily available starting materials.[20-23] Recently, we reported a Rh(III)-catalyzed formal [4+1] approach to pyrrolidines from simple unactivated terminal alkenes and nitrene sources.[24] Mechanistic investigations led us to propose a Rh-catalyzed intermolecular aziridination with subsequent ring expansion by triflic acid for the synthesis of 5-membered saturated *N*-heterocycle. Motivated by the fact that aziridine formation is highly efficient in this system, we envisioned that this intermediate can be utilized for the one-pot synthesis of vicinal diamines in the presence of exogenous nitrogen nucleophiles.

5.2 Reaction development

In order to test this idea, we added morpholine (**2a**) as amine nucleophile after the initial aziridination of 1-hexene (**1a**) and 4-methyl-*N*-(pivaloyloxy)benzenesulfonamide (Ts-NH-OPiv) in the presence of a catalytic amount of Cs_2CO_3 (0.1 equiv) and $[Ind^*RhCl_2]_2$ catalyst (2.5 mol%) in HFIP. Preliminary results showed that when 2 equiv. of morpholine was added and stirred at room temperature and 40 °C, desired diamination products were formed as a single regioisomer albeit low yield (**Table 5.1**. entry 1, 2). Increasing reaction temperature to 80 °C further improved the reaction yield to 63% (entry 3). Since we observed unreacted aziridine on workup, longer reaction time and higher concentration were applied to complete the reaction, and the yield of **3aa** improved to 87% when the reaction was conducted at 80 °C for 16 hours in 0.2 M of HFIP (entry

6). Lewis acid-promoted aziridine ring opening by amines is well-known;[20-23] however, adding $AgSbF_6$ together with morpholine after aziridination gives a lower yield of **3aa** (entry 4). Finally, a quantitative yield of the desired product is observed at 0.2 M with 3 equiv. of morpholine (entry 7).



entry	conc. (M)	morpholine (equiv)	temp.(°C)	reaction time (h)	yield (%)[a]
1	0.1	2	22	8	< 5
2	0.1	2	40	8	19
3	0.1	2	80	8	63
4[b]	0.1	2	80	8	28
5	0.1	2	80	20	78
6	0.2	2	80	20	87
7	**0.2**	**3**	**80**	**24**	**99**

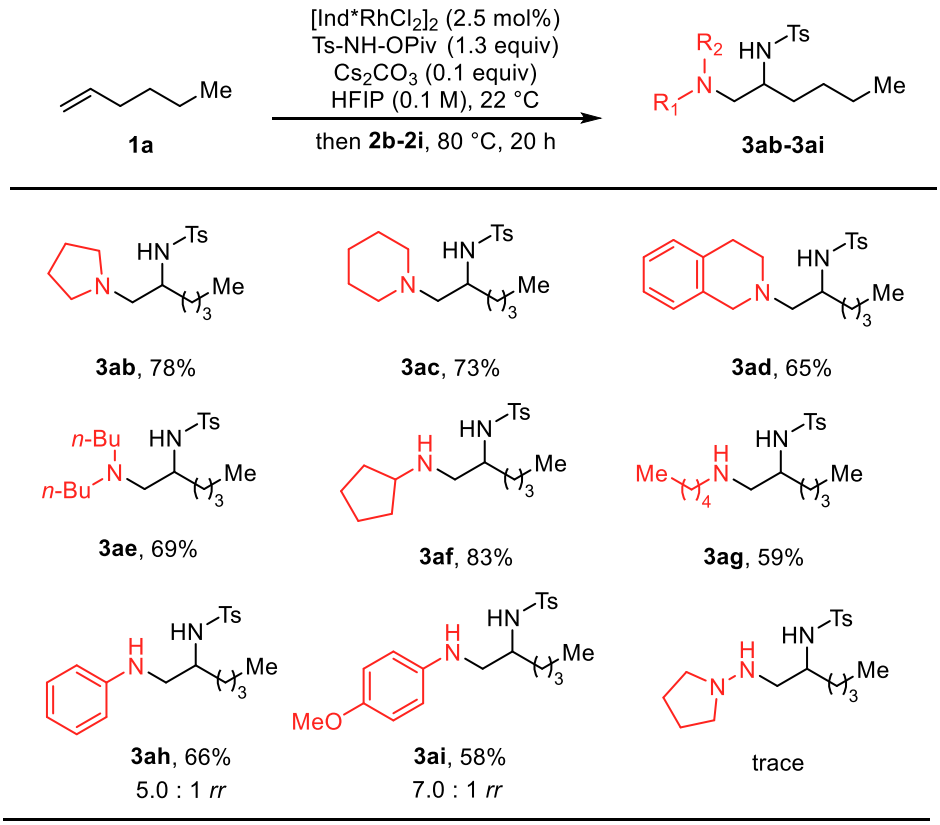
[a]Determined by ^{1}H NMR analysis of unpurified reaction mixture.
[b]$AgSbF_6$ (1 equiv) was added.

Table 5.1: Optimization table.

5.3 Reaction scope

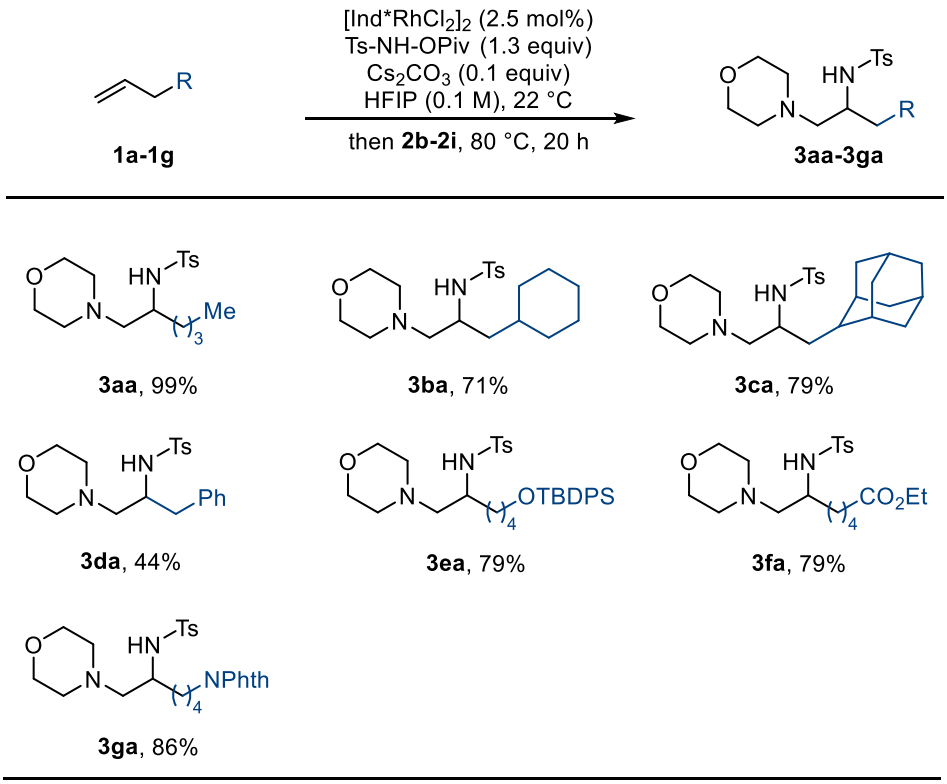
Having optimized the reaction conditions, we next sought to explore the scope of this methodology. First, various commercially available primary and secondary amines were examined using 1-hexene as an alkene coupling partner (**Scheme 5.3**). Cyclic secondary amines such as

pyrrolidine (**2b**) and piperidine (**2c**) provide diamination products with good yield (**3ab**, **3ac**). Bicyclic 1,2,3,4-tetrahydroisoquinoline (**2d**) also works well as a nucleophile giving 65% of corresponding 1,2-diamine (**3ad**). The reaction with dibutyl amine also delivers 1,2-vicinal diamine product with a good yield (**3ae**). The reaction also proceeds smoothly with primary amines, giving desired products (**3af**-**3ai**) in good yield. When aniline (**2h**) and 4-methoxyaniline (**2i**) are used as a nucleophile, the minor regioisomer is also observed in small amounts. Hydrazine-type nucleophile (1-aminopyrrolidine) was also tested but only trace amount of desired product was observed.



Scheme 5.3: Amine nucleophile substrate scope.

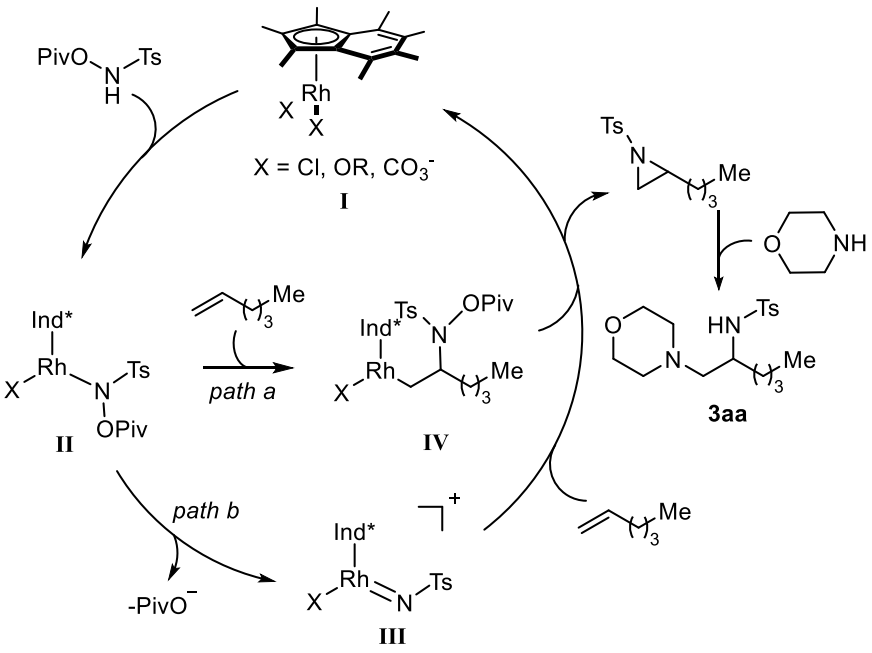
Next, we tested the synthetic utility of this method with a variety of terminal unactivated alkene substrates (**Scheme 5.4**). Allyl cyclohexane and 2-allyladamantane are successfully converted to the corresponding diamination products in good yield (**3ba**, **3ca**). A variety of functional groups such as phenyl (**3da**), *tert*-butyldiphenylsilyl protected alcohol (**3ea**), ethyl ester (**3fa**), and protected amine (**3ga**) are all well tolerated, giving the desired 1,2-diamination product in good yield.



Scheme 5.4: Alkene substrate scope.

5.4 Proposed mechanism

Based on our previous work[24] and aziridine ring-opening precedent,[20-23] we propose the following mechanism for the reaction. First, $[Ind^*RhCl_2]_2$ catalyst metalates Ts-NH-OPiv to generate Rh complex **II**, which undergoes Rh-nitrene formation to yield intermediate **III**. Subsequent aziridination with an unactivated alkene coupling partner (**1a**) would give aziridine intermediate with the regeneration of active Rh(III) catalyst. Alternatively, the alkene coupling partner (**1a**) can coordinate with Rh complex **II** and undergoes alkene migratory insertion to form complex **IV**. Subsequent C-N bond formation and N-O bond cleavage would generate an aziridine intermediate. Nucleophilic attack of primary and/or secondary amines on the less hindered terminal carbon of an aziridine produces diamination products at elevated temperature.



Scheme 5.5: Proposed mechanism.

5.5 Summary

In summary, we demonstrate the one-pot synthesis of vicinal diamines from readily available α-olefins through Rh(III)-catalyzed aziridination and subsequent nucleophilic attack by exogenous amines. The reaction exhibits broad functional group tolerance with good yield and regioselectivity.[25]

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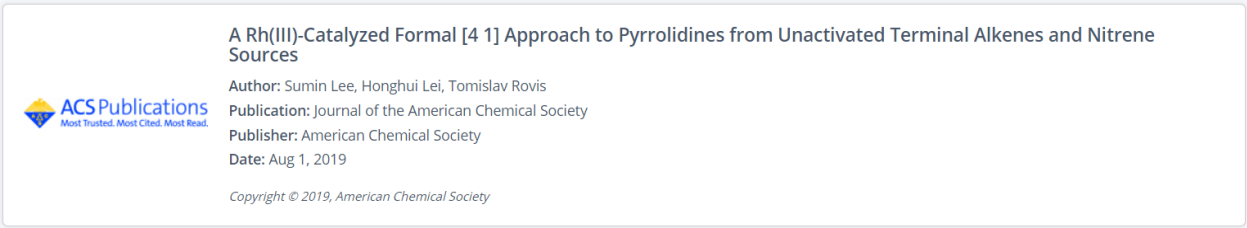
Appendix A

SUPPLEMENTARY DATA FOR CHAPTER TWO



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Supporting Information

A Rh(III)-Catalyzed Formal [4+1] Approach to Pyrrolidines from Unactivated Terminal Alkenes and Nitrene Sources

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Contents

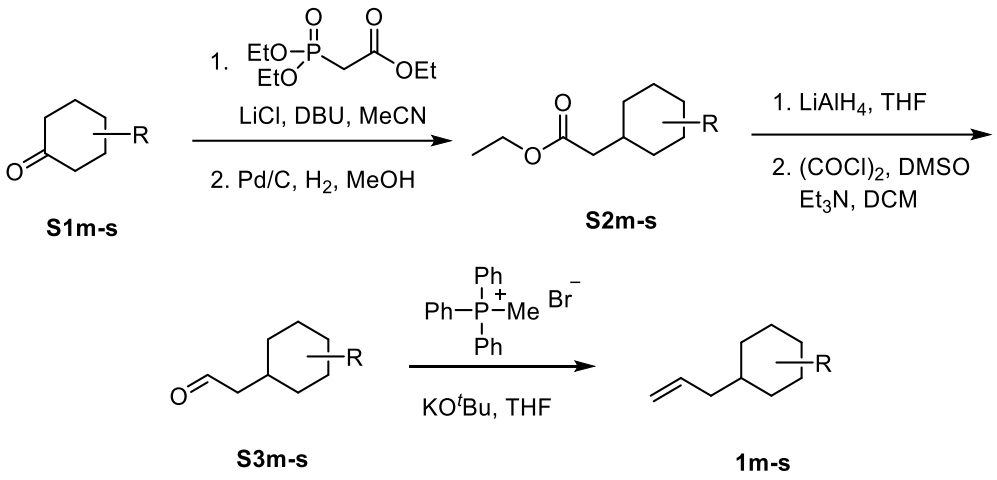
1. General Information

All reactions were carried out using oven-dried glassware with magnetic stirring unless otherwise noted. Anhydrous solvents and reagents were purchased from commercial sources and used without further purification except HFIP which was distilled with 3 Å molecular sieves. Flash chromatography was conducted either manually on SiliCycle® SilicaFlash® P60 (230-400 mesh) silica gel, SiliCycle® prep TLC (TLG-R10011B-341, thickness 1000um) or automatically *via* a Teledyne Isco Lumen CombiFlash with RediSep Rf Disposable Flash columns. Thin layer chromatography (TLC) was performed on Silicycle 250μm silica gel 60 Å plates. Visualization was accomplished with UV light (254 nm) and $KMnO_4$. ^1H, ^{19}F NMR and ^{13}C NMR spectra were collected at ambient temperature on Bruker 400 MHz and Bruker Avance III 500 MHz spectrometers unless otherwise noted. Chemical shifts (δ) are reported in parts per million (ppm), coupling constants (J) are reported in Hz, and multiplicity is described using the following abbreviations: singlet (s), broad (b), multiplet (m), doublet (d), triplet (t), quartet (q), or combinations thereof. ^1H NMR spectra were referenced to 7.26 ppm ($CHCl_3$). ^{13}C NMR spectra were referenced to 77.16 ppm ($CDCl_3$) and all peaks given are singlet unless otherwise noted. Diastereomeric and regioisomeric ratios were measured by integration of ^1H NMR spectra of product mixtures prior to purification. Low resolution mass spectra were recorded on a Waters Acquity HuPLC-MS or Agilent 5977B GC/MS. Infrared spectra were collected on a Perkin Elmer Spectrum Two FT-IR Spectrometer. Melting point were measured by Stanford Research System MPA160 melting point apparatus.

2. Preparation of Starting Materials

1a, **1b**, **1c**, **1e**, **1f** and **1l** were purchased from Sigma Aldrich and used without further purification. **1d**,[1] **1g-i**,[2] **1j**,[3] **1k**,[4] **2a-b**,[5] and $[Ind^*RhCl_2]_2$ catalyst[6] were synthesized following literatures. Allyl cyclohexanes (**1m**, **1n**, **1o**, **1p**, **1q**, **1r, 1s**) were synthesized following general procedures below.

General Procedure: synthesis of allyl cyclohexanes



To a suspension of LiCl (1.42 equiv) in MeCN (1.0 M) were added DBU (1.21 equiv) and triethyl phosphonoacetate (1.30 equiv) at 0 °C. The mixture was stirred at 0 °C for 30 minutes, before cyclohexanone (**S1m-s**) (1 equiv) was added. The reaction was stirred at room temperature overnight and quenched by the addition of saturated aqueous solution of $NaHCO_3$. The mixture was extracted with ethyl acetate three times. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate) to afford the corresponding α,β-unsaturated ester (**S2m-s**).

The α, β-unsaturated ester (**S2m-s**) was then dissolved in MeOH (0.3 M) and Pd/C (10% wt) was added at room temperature. The reaction mixture was stirred under atmospheric H_2 overnight before filtered through celite and concentrated under vacuum. The crude product was used without further purification.

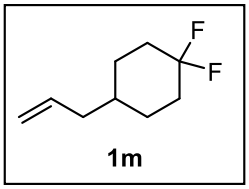
Ester (**S2m-s**) was added dropwise to a suspension of $LiAlH_4$ (2 equiv) in THF (0.2 M) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 - 4 hours. After completion of the reaction, the mixture was subsequently added x mL water, x mL 15% aqueous solution of NaOH and 3x mL additional water (x = g of $LiAlH_4$ used). The resulting mixture was then dried with anhydrous $MgSO_4$, filtered through celite and concentrated to give the crude alcohol.

To a solution of oxalyl chloride (1.3 equiv) in DCM (0.2 M) at -78 °C was added DMSO (2 equiv) and the crude alcohol (1 equiv). The solution was stirred for 30 min before Et_3N (3 equiv) was added slowly over 30 minutes. The mixture was warmed to room temperature and stirred for additional 30 minutes. The reaction was quenched with water and extracted with DCM. The combined organic layers were washed

with brine, dried over anhydrous $MgSO_4$, filtered through celite and concentrated. The resulting aldehyde (**S3m-s**) was used without further purification.

Potassium *tert*-butoxide (1.7 equiv) was added to a suspension of methyltriphenylphosphonium bromide (2 equiv) in THF (0.2 M) at 0 °C. After the solution was stirred for 1 hour at this temperature, the crude aldehyde (**S2m-s**) in THF was added dropwise. The reaction was warmed to room temperature and stirred overnight. Pentane was added to the reaction mixture and the suspension was filtered through a short plug of silica. The mixture was purified by chromatography on silica gel (pentane) to afford the corresponding allyl cyclohexane (**1m-s**).

4-allyl-1,1-difluorocyclohexane (**1m**)



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (ddt, J = 16.3, 11.0, 7.1 Hz, 1H), 5.09 – 4.90 (m, 2H), 2.11 – 1.97 (m, 4H), 1.81 – 1.61 (m, 4H), 1.47 – 1.34 (m, 1H), 1.32 – 1.20 (m, 2H).

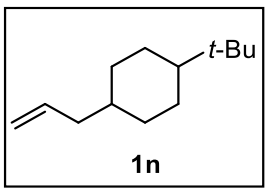
^{13}C NMR (126 MHz, $CDCl_3$) δ 136.9, 123.9 (dd, J = 241.9, 239.6 Hz), 116.3, 40.3 (d, J = 2.7 Hz), 35.8 (d, J = 1.5 Hz), 33.6 (dd, J = 25.4, 22.4 Hz), 28.8 (d, J = 9.5 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) δ -90.7 (d, J = 234.8 Hz), -100.9 (d, J = 236.3 Hz).

IR ($CDCl_3$, cm^{-1}) ν 3078, 2939, 2866, 2254, 1835, 1651, 1448, 1114, 963, 906, 728, 650, 605.

LRMS (EI) m/z [$C_9H_{14}F_2$] calculated 160.1, found 160.1.

1-allyl-4-(*tert*-butyl)cyclohexane (**1n**)



3.1:1 *dr*

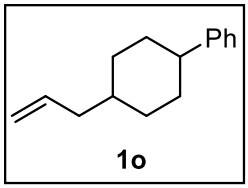
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 – 5.72 (m, 1H, 2 dias.), 5.04 – 4.92 (m, 2H, 2 dias.), 2.12 – 2.07 (m, 2H, minor), 1.97 – 1.91 (m, 2H, major), 1.83 – 1.70 (m, 4H, major, 1H, minor), 1.69 – 1.63 (m, 2H, minor), 1.52 – 1.47 (m, 2H, minor), 1.46 – 1.38 (m, 2H, minor), 1.29 – 1.17 (m, 1H, major), 1.12 (qd, *J* = 12.5, 3.3 Hz, 2H, minor), 1.02 – 0.88 (m, 5H, major, 1H, minor), 0.84 (s, 9H, minor), 0.83 (s, 9H, major).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8, 138.0, 115.3, 115.1, 48.6, 48.3, 42.0, 38.0, 35.8, 33.7, 32.7, 32.6, 32.5, 30.3, 27.8, 27.7, 27.4, 21.7.

IR ($CDCl_3$, cm^{-1}) *v* 3076, 2938, 2917, 2856, 2251, 1822, 1650, 1448, 1365, 1236, 993, 906, 733, 650.

LRMS (EI) m/z [$C_{13}H_{24}$] calculated 180.2, found 180.2.

(4-allylcyclohexyl)benzene (**1o**)



1o

2.8:1 *dr*

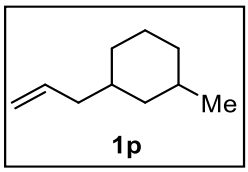
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.15 (m, 5H, 2 dias.), 5.89 – 5.76 (m, 1H, 2 dias.), 5.07 – 4.97 (m, 2H, 2 dias.), 2.59 (tt, *J* = 9.4, 4.9 Hz, 1H, Minor), 2.47 (tt, *J* = 12.3, 3.3 Hz, 1H, major), 2.19 (tt, *J* = 7.4, 1.3 Hz, 2H, minor), 2.02 (tt, *J* = 7.0, 1.3 Hz, 2H, major), 1.96 – 1.85 (m, 4H, major), 1.84 – 1.77 (m, 1H, minor), 1.74 – 1.59 (m, 8H, minor), 1.54 -1.43 (m, 2H, major), 1.43 – 1.35 (m, 1H, major) 1.15 – 1.04 (m, 2H, major)

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.9, 147.6, 138.3, 137.7, 128.4, 128.4, 127.1, 127.0, 126.0, 125.9, 115.6, 115.5, 44.6, 43.6, 42.0, 37.5, 36.6, 34.4, 33.4, 33.0, 29.8, 28.9.

IR ($CDCl_3$, cm^{-1}) *v* 3076, 3061, 3026, 2976, 2920, 2851, 2248, 1638, 1601, 1492, 1447, 1080, 1066, 1030, 995, 969, 905, 728, 698, 649, 584, 530.

LRMS (EI) m/z [$C_{15}H_{20}$] calculated 200.2, found 200.2.

1-allyl-3-methylcyclohexane (**1p**)



1p

3.0:1 *dr*

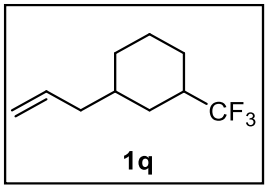
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 – 5.73 (m, 1H, 2 dias.), 5.01 – 4.93 (m, 2H, 2dias.), 2.04 – 1.99 (m, 2H, minor), 1.99 – 1.89 (m, 2H, major), 1.79 – 1.08 (m, 8H, 2dias.), 0.89 (d, *J* = 6.9 Hz, 3H, minor), 0.87 (d, *J* = 6.5 Hz, 3H, major), 0.79 (m, 2H, major), 0.54 (m, 2H, minor).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4, 137.9, 115.3, 115.2, 42.2, 42.1, 39.4, 39.0, 37.9, 35.4, 33.9, 32.9, 32.8, 32.5, 31.4, 27.3, 26.5, 23.1, 20.9, 20.9.

IR ($CDCl_3$, cm^{-1}) ν 3075, 2920, 2853, 1639, 1456, 1376, 995, 906, 733, 650.

LRMS (EI) m/z [$C_{10}H_{18}$] calculated 138.1, found 138.1.

1-allyl-3-(trifluoromethyl)cyclohexane (**1q**)



1q

3.8:1 *dr*

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 – 5.69 (m, 1H, 2 dias.), 5.05 – 4.97 (m, 2H, 2dias.), 2.25 – 1.73 (m, 7H), 1.67 – 1.30 (m, 2H), 1.29 – 0.82 (m, 3H).

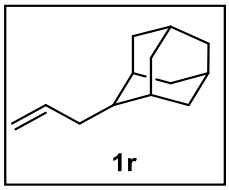
^{13}C NMR (126 MHz, $CDCl_3$) δ 137.3, 136.7, 128.5 (q, *J* = 279.3 Hz), 127.9 (q, *J* = 278.6 Hz), 116.3, 116.1, 42.2 (q, *J* = 26.4 Hz), 41.7, 37.3, 36.9 (q, *J* = 26.0 Hz), 36.7, 32.2, 31.9, 31.2 (q, *J* = 2.6 Hz), 29.5, 28.8 (q, *J* = 2.4 Hz), 25.1 (q, *J* = 2.6 Hz), 25.0 (q, *J* = 2.5 Hz), 24.9, 20.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ -72.2 (d, *J* = 9.3 Hz), -74.0 (d, *J* = 8.5 Hz).

IR ($CDCl_3$, cm^{-1}) *v* 3078, 2938, 2863, 2254, 1641, 1465, 1448, 1391, 1323, 1285, 1258, 1202, 1167, 995, 907, 732, 650.

LRMS (EI) m/z [$C_{10}H_{15}F_3$] calculated 192.1, found 192.1.

2-allyladamantane (**1r**)



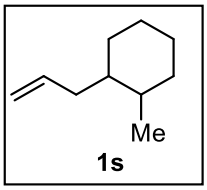
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddt, J = 17.1, 10.1, 7.1 Hz, 1H), 5.04 – 4.93 (m, 2H), 2.20 (tt, J = 7.2, 1.4 Hz, 2H), 1.91 – 1.78 (m, 6H), 1.76 – 1.67 (m, 7H), 1.54 – 1.47 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 115.0, 44.3, 39.4, 38.6, 37.5, 31.6, 28.5, 28.23.

IR ($CDCl_3$, cm^{-1}) v 3074, 2973, 2904, 2850, 2661, 2250, 1638, 1454, 1100, 994, 904, 728, 650, 607.

LRMS (EI) m/z [$C_{13}H_{20}$] calculated 176.2, found 176.2.

1-allyl-2-methylcyclohexane (**1s**)



1.6:1 *dr*

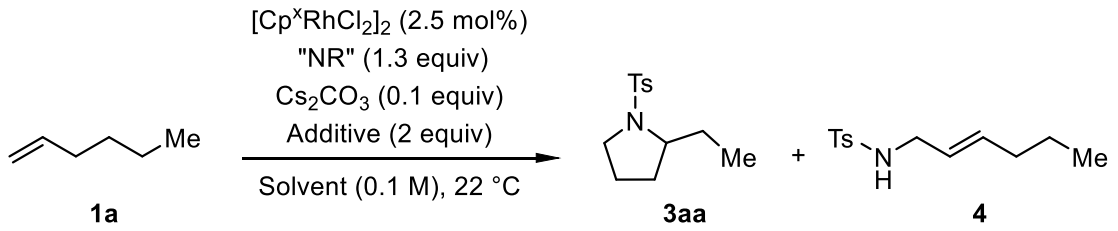
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 – 5.72 (m, 1H, 2 dias.), 5.04 – 4.92 (m, 2H, 2 dias.), 2.33 – 2.26 (m, 1H, minor), 2.20 – 0.93 (m, 11H, 2 dias.), 1.84 – 1.76 (m, 1H, major), 0.91 (d, J = 6.4 Hz, 3H, major.), 0.84 (d, J = 7.1 Hz, 3H, major).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4, 137.9, 115.3, 115.2, 42.2, 42.1, 39.4, 39.0, 37.9, 35.4, 33.9, 32.9, 32.8, 32.5, 31.4, 27.3, 26.5, 23.1, 20.9, 20.9.

IR ($CDCl_3$, cm^{-1}) v 3080, 2923, 2853, 1639, 1447, 1382, 996, 907, 734, 650.

LRMS (EI) m/z [$C_{10}H_{18}$] calculated 138.1, found 138.1.

3. Detailed Optimization Table

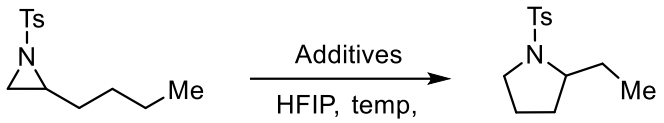


1a **3aa** **4**

entry	"Nitrene source"	Cp^X	Solvent	Additive	yield of **3aa** (%)[a]	yield of **4** (%)[a]
1[b]	Ts-NH-OPiv (**2a**)	Ind*	HFIP	AgOTf	15	15
2	Ts-NH-OPiv (**2a**)	Ind*	HFIP	AgOTf	0 (50)[c]	-
3	Ts-NH-OPiv (**2a**)	Ind*	HFIP	$Sc(OTf)_3$	45 (58)[c]	-
4	Ts-NH-OPiv (**2a**)	Ind*	HFIP	TfOH	66	-
5	Ts-NH-OPiv (**2a**)	Cp*	HFIP	TfOH	15	-
6	3-phenyl-1,4,2-dioxazol-5-one	Ind*	HFIP	TfOH	0	-
7	$Ts\text{-}N_3$	Ind*	HFIP	TfOH	0	-
8	Ts-NH-OPiv (**2a**)	Ind*	DCE	TfOH	0	-
9	Ts-NH-OPiv (**2a**)	Ind*	AcOH	TfOH	0	-
10	Ts-NH-OPiv (**2a**)	Ind*	MeCN	TfOH	0	-
11	Ts-NH-OPiv (**2a**)	Ind*	THF	TfOH	0	-
12	Ts-NH-OPiv (**2a**)	Ind*	Toluene	TfOH	0	-
13	Ts-NH-OPiv (**2a**)	Ind*	1,4-dioxane	TfOH	0	-
14	Ts-NH-OPiv (**2a**)	Ind*	Acetone	TfOH	0	-
15	Ts-NH-OPiv (**2a**)	Ind*	DMF	TfOH	0	-
16	Ts-NH-OPiv (**2a**)	Cp^t	HFIP	TfOH	trace	-
17	Ts-NH-OPiv (**2a**)	Cp^{*CF3}	HFIP	TfOH	40	-
18	Ts-NH-OPiv (**2a**)	Cp^{*Ph}	HFIP	TfOH	17	-
19	Ts-NH-OPiv (**2a**)	Cp^{*iPr}	HFIP	TfOH	10	-

Reactions were conducted on a 0.1 mmol scale using **1a** (1.0 equiv). Additive was added after 24 h. [a]Determined by analysis of ^1H NMR of the unpurified reaction mixture. [b]Reaction was conducted at 40 °C with 1 equiv of **2a** and the additive (40 mol%) was added initially. [c]Reaction temperature increased to 80 °C after addition of additive. Ind* = heptamethylindenyl, Cp^t = di-*tert*-butylcyclopentadienyl, Cp^{*CF3} = tetramethyl(trifluoromethyl)cyclopentadienyl, Cp^{*Ph} = phenyltetramethylcyclopentadienyl, Cp^{*iPr} = isopropyltetramethylcyclopentadienyl.

Optimization Table-2: from aziridine to pyrrolidine:



temp (°C)	conc.	Additive	yield (%)
80	0.5 M	AgOTf (40 mol%)	12
80	0.5 M	$Sc(OTf)_3$ (40 mol%)	63
80	0.5 M	$Bi(OTf)_3$ (40 mol%)	64
80	0.5 M	$In(OTf)_3$ (40 mol%)	64
80	0.5 M	$Mg(OTf)_2$ (40 mol%)	57
80	0.5 M	$Ni(OTf)_2$ (40 mol%)	14
80	0.5 M	$Sn(OTf)_2$ (40 mol%)	60
80	0.5 M	$Zn(OTf)_2$ (40 mol%)	10
80	0.5 M	$Y(OTf)_3$ (40 mol%)	19
80	0.5 M	$Gd(OTf)_3$ (40 mol%)	17
80	0.5 M	TfOH (40 mol%)	51
40	0.1 M	TfOH (100 mol%)	68
rt	0.1 M	TfOH (200 mol%)	75

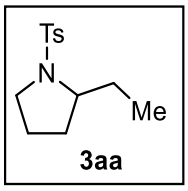
4. General Procedure for Pyrrolidine Synthesis

Cesium carbonate (0.01 mmol, 0.1 equiv), *N*-(pivaloyloxy)sulfonamide (0.13 mmol, 1.3 equiv) were measured in an oven-dried 1 dram vial with a magnetic stir bar in the glovebox. In a separate vial, alkene (0.1 mmol, 1 equiv) was dissolved in 0.35 mL of HFIP and transferred to the first vial. It was rinsed with additional 0.35 mL of HFIP and transferred again to the first vial. (In case of volatile alkenes **1a**, **1b**, and **1e**, Cesium carbonate and *N*-(pivaloyloxy)sulfonamide were dissolved in 0.7 mL of HFIP and the alkene was added directly using micropipette). $[Ind^*RhCl_2]_2$ (0.0025 mmol, 2.5 mol%) in 0.3 mL of HFIP was added to the first vial and stirred at 22 °C for 24 hours. Triflic acid (0.2 mmol, 2 equiv) was added to the reaction mixture and stirred for additional 24 hours. Reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and extracted 3 times with DCM. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solid was filtered and the filtrate was concentrated by rotary evaporator. A crude ^1H NMR spectrum was collected with 1,3,5-trimethoxybenzene as the internal

standard. Purification was performed by flash chromatography or preparational TLC using ethyl acetate and hexane as the eluent.

5. Product Characterization

2-Ethyl-1-tosylpyrrolidine (**3aa**)



3aa

Yield: 61%, white solid. m.p. 72 – 74 °C

R_f = 0.26 (EA/Hex 1:8).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.69 (m, 2H), 7.33 – 7.28 (m, 2H), 3.57 – 3.50 (m, 1H), 3.37 (ddd, *J* = 10.4, 7.1, 5.2 Hz, 1H), 3.18 (dt, *J* = 10.4, 7.2 Hz, 1H), 2.42 (s, 3H), 1.89 – 1.81 (m, 1H), 1.80 – 1.72 (m, 1H), 1.60 – 1.52 (m, 2H), 1.52 – 1.43 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H).

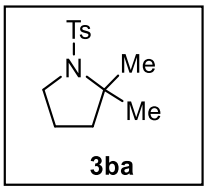
^{13}C NMR (126 MHz, $CDCl_3$) δ 143.3, 135.2, 129.7, 127.6, 62.0, 49.1, 30.3, 29.3, 24.3, 21.7, 10.5.

The spectral data are consistent with those reported in the literature[7]

IR ($CDCl_3$, cm^{-1}) *v* 3059, 2969, 2933, 2876, 1341, 1159, 1093, 737, 663, 587, 550.

LRMS (ESI+APCI) m/z $[C_{13}H_{20}NO_2S]^+$ ($[M+H]^+$) calculated 254.1, found 254.1.

2,2-Dimethyl-1-tosylpyrrolidine (**3ba**)



3ba

Yield: 63%, white solid. m.p. 80 – 82 °C

R_f = 0.20 (EA/Hex 1:8).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 – 7.70 (m, 2H), 7.28 – 7.23 (m, 2H), 3.38 (t, *J* = 6.5 Hz, 2H), 2.40 (s, 3H), 1.83 – 1.74 (m, 4H), 1.43 (s, 6H).

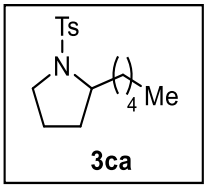
^{13}C NMR (126 MHz, $CDCl_3$) δ 142.6, 138.9, 129.5, 127.3, 65.2, 49.5, 43.1, 28.4, 22.6, 21.6.

The spectral data are consistent with those reported in the literature[8]

IR ($CDCl_3$, cm^{-1}) ν 2969, 2873, 1599, 1333, 1153, 1095, 1008, 816, 678, 591, 549.

LRMS (ESI+APCI) m/z $[C_{13}H_{20}NO_2S]^+$ ($[M+H]^+$) calculated 254.1, found 254.1.

2-pentyl-1-tosylpyrrolidine (**3ca**)



3ca

Yield: 54%, yellowish oil.

R_f = 0.29 (EA/Hex 1:8).

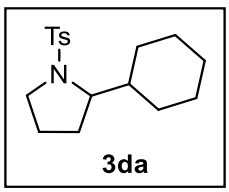
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.68 (m, 2H), 7.32 – 7.27 (m, 2H), 3.59 (dq, J = 11.9, 4.9 Hz, 1H), 3.37 (ddd, J = 11.1, 7.0, 5.4 Hz, 1H), 3.18 (dt, J = 10.5, 7.2 Hz, 1H), 2.42 (s, 3H), 1.87 – 1.71 (m, 2H), 1.60 – 1.51 (m, 2H), 1.51 – 1.39 (m, 2H), 1.37 – 1.23 (m, 6H), 0.88 (t, J = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.3, 135.2, 129.7, 127.6, 60.8, 49.0, 36.6, 31.9, 30.8, 26.0, 24.3, 22.8, 21.7, 14.2.

IR ($CDCl_3$, cm^{-1}) ν 2956, 2928, 2860, 2255, 1598, 1494, 1458, 1339, 1197, 1159, 1093, 906, 815, 730.

LRMS (ESI+APCI) m/z $[C_{16}H_{26}NO_2S]^+$ ($[M+H]^+$) calculated 296.2, found 296.1.

2-cyclohexyl-1-tosylpyrrolidine (**3da**)



3da

Yield: 49%, white solid. m.p. 113 – 115 °C

R_f = 0.25 (EA/Hex 1:9).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.69 (m, 2H), 7.32 – 7.27 (m, 2H), 3.56 – 3.48 (m, 1H), 3.27 (t, *J* = 6.5 Hz, 2H), 2.42 (s, 3H), 1.79 – 1.61 (m, 8H), 1.45 – 1.32 (m, 2H), 1.28 – 1.06 (m, 3H), 1.03 – 0.86 (m, 2H).

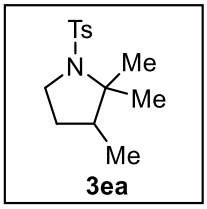
^{13}C NMR (126 MHz, $CDCl_3$) δ 143.2, 135.4, 129.7, 127.7, 65.3, 49.3, 42.4, 30.6, 27.7, 27.1, 26.7, 26.5, 26.3, 24.7, 21.7.

The spectral data are consistent with those reported in the literature[9]

IR ($CDCl_3$, cm^{-1}) *v* 3056, 2927, 2853, 1598, 1340, 1265, 1158, 1092, 735, 665.

LRMS (ESI+APCI) m/z $[C_{17}H_{26}NO_2S]^+$ ($[M+H]^+$) calculated 308.2, found 308.1.

2,2,3-Trimethyl-1-tosylpyrrolidine (**3ea**)



3ea

Yield: 75%, white solid. m.p. 92 – 94 °C

R_f = 0.22 (EA/Hex 1:15).

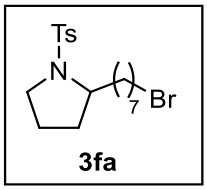
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.68 (m, 2H), 7.28 – 7.21 (m, 2H), 3.54 – 3.47 (m, 1H), 3.18 (ddd, *J* = 10.3, 9.1, 6.6 Hz, 1H), 2.40 (s, 3H), 1.88 – 1.78 (m, 2H), 1.57 – 1.46 (m, 1H), 1.40 (s, 3H), 1.18 (s, 3H), 0.88 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6, 139.1, 129.4, 127.2, 67.2, 47.2, 45.7, 30.1, 26.8, 22.5, 21.6, 13.9.

IR ($CDCl_3$, cm^{-1}) *v* 3057, 2971, 2879, 1330, 1266, 1154, 1094, 737, 705, 676, 600, 550.

LRMS (ESI+APCI) m/z $[C_{14}H_{22}NO_2S]^+$ ($[M+H]^+$) calculated 268.1, found 268.1.

2-(7-bromoheptyl)-1-tosylpyrrolidine (**3fa**)



3fa

Yield: 55%, yellow oil.

R_f = 0.29 (EA/Hex 1:8).

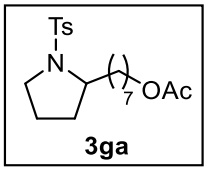
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.68 (m, 2H), 7.32 – 7.28 (d, J = 8.0 Hz, 2H), 3.63 – 3.54 (m, 1H), 3.41 (t, J = 6.8 Hz, 2H), 3.37 (ddd, J = 10.4, 7.0, 5.1 Hz, 1H), 3.18 (dt, J = 10.4, 7.2 Hz, 1H), 2.42 (s, 3H), 1.90 – 1.70 (m, 4H), 1.62 – 1.51 (m, 2H), 1.51 – 1.38 (m, 4H), 1.37 – 1.26 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.3, 135.1, 129.7, 127.6, 60.7, 49.0, 36.5, 34.2, 32.9, 30.8, 29.4, 28.8, 28.2, 26.1, 24.3, 21.7.

IR ($CDCl_3$, cm^{-1}) v 2928, 2856, 1597, 1461, 1343, 1159, 1092, 815, 736, 664, 587, 551.

LRMS (ESI+APCI) m/z $[C_{18}H_{29}BrNO_2S]^+$ ($[M+H]^+$) calculated 402.1 & 404.1, found 402.1 & 404.1.

7-(1-tosylpyrrolidin-2-yl)heptyl acetate (**3ga**)



3ga

Yield: 55%, yellow oil.

R_f = 0.38 (EA/Hex 1:4).

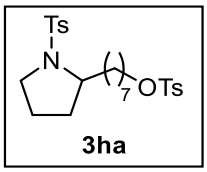
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.68 (m, 2H), 7.32 – 7.28 (m, 2H), 4.05 (t, J = 6.8 Hz, 2H), 3.61 – 3.55 (m, 1H), 3.36 (ddd, J = 10.4, 7.1, 5.1 Hz, 1H), 3.18 (dt, J = 10.4, 7.2 Hz, 1H), 2.42 (s, 3H), 2.04 (s, 3H), 1.85 – 1.70 (m, 2H), 1.66 – 1.58 (m, 2H), 1.58 – 1.51 (m, 2H), 1.51 – 1.39 (m, 2H), 1.38 – 1.26 (m, 8H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 143.3, 135.2, 129.7, 127.6, 64.7, 60.7, 49.0, 36.6, 30.8, 29.6, 29.3, 28.7, 26.2, 26.0, 24.3, 21.6, 21.2.

IR ($CDCl_3$, cm^{-1}) v 3057, 2931, 2858, 1733, 1598, 1342, 1265, 1247, 1159, 1092, 816, 736, 664.

LRMS (ESI+APCI) m/z $[C_{20}H_{32}NO_4S]^+$ ($[M+H]^+$) calculated 382.2, found 382.2.

7-(1-tosylpyrrolidin-2-yl)heptyl 4-methylbenzenesulfonate (**3ha**)



3ha

Yield: 57%, yellow oil.

R_f = 0.12 (EA/Hex 1:8).

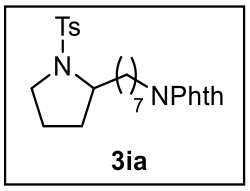
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.77 (m, 2H), 7.72 – 7.68 (m, 2H), 7.37 – 7.33 (m, 2H), 7.32 – 7.28 (m, 2H), 4.02 (t, *J* = 6.5 Hz, 2H), 3.60 – 3.53 (m, 1H), 3.36 (ddd, *J* = 10.4, 7.1, 5.1 Hz, 1H), 3.17 (dt, *J* = 10.4, 7.2 Hz, 1H), 2.45 (s, 3H), 2.42 (s, 3H), 1.83 – 1.70 (m, 2H), 1.67 – 1.59 (m, 2H), 1.58 – 1.50 (m, 2H), 1.50 – 1.37 (m, 2H), 1.32 – 1.20 (m, 8H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.8, 143.3, 135.1, 133.3, 130.0, 129.7, 128.0, 127.6, 70.8, 60.6, 49.0, 36.5, 30.8, 29.4, 29.0, 28.9, 26.0, 25.4, 24.2, 21.8, 21.6.

IR ($CDCl_3$, cm^{-1}) ν 3061, 2928, 2858, 1598, 1461, 1343, 1188, 1176, 1158, 1095, 815, 736, 664, 587, 553.

LRMS (ESI+APCI) m/z $[C_{25}H_{36}NO_5S_2]^+$ ($[M+H]^+$) calculated 494.2, found 494.2.

2-(7-(1-tosylpyrrolidin-2-yl)heptyl)isoindoline-1,3-dione (**3ia**)



3ia

Yield: 52%, yellow oil.

R_f = 0.16 (EA/Hex 1:4).

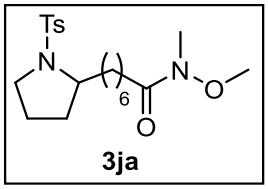
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.80 (m, 2H), 7.75 – 7.65 (m, 4H), 7.32 – 7.27 (m, 2H), 3.72 – 3.63 (m, 2H), 3.61 – 3.53 (m, 1H), 3.35 (ddd, *J* = 10.4, 7.0, 5.1 Hz, 1H), 3.18 (dt, *J* = 10.4, 7.1 Hz, 1H), 2.41 (s, 3H), 1.86 – 1.71 (m, 2H), 1.71 – 1.61 (m, 2H), 1.60 – 1.50 (m, 2H), 1.50 – 1.38 (m, 2H), 1.37 – 1.23 (m, 8H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 143.2, 135.2, 134.0, 132.3, 129.7, 127.6, 123.3, 60.7, 49.0, 38.2, 36.5, 30.8, 29.5, 29.3, 28.7, 26.9, 26.2, 24.3, 21.6.

IR ($CDCl_3$, cm^{-1}) *ν* 2931, 2858, 2255, 1771, 1709, 1598, 1397, 1337, 1158, 1092, 907, 727, 664, 649.

LRMS (ESI+APCI) m/z $[C_{26}H_{33}N_2O_4S]^+$ ($[M+H]^+$) calculated 469.2, found 469.2.

N-methoxy-*N*-methyl-7-(1-tosylpyrrolidin-2-yl)heptanamide (**3ja**)



3ja

Yield: 53%, yellow oil.

$\mathbf{R_f}$ = 0.33 (EA/Hex 1:1).

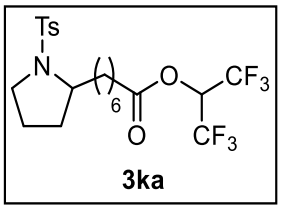
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.70 (m, 2H), 7.33 – 7.27 (m, 2H), 3.68 (s, 3H), 3.60 – 3.53 (m, 1H), 3.36 (ddd, J = 10.4, 7.1, 5.1 Hz, 1H), 3.21 – 3.12 (m, 4H), 2.42 (s, 5H), 1.87 – 1.78 (m, 1H), 1.78 – 1.70 (m, 1H), 1.68 – 1.57 (m, 2H), 1.57 – 1.50 (m, 2H), 1.49 – 1.40 (m, 2H), 1.38 – 1.26 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 143.3, 135.1, 129.7, 127.6, 61.4, 60.7, 49.0, 36.5, 32.3, 32.0, 30.8, 29.5, 29.4, 26.1, 24.7, 24.2, 21.6.

IR ($CDCl_3$, cm^{-1}) ν 3054, 2936, 2858, 1657, 1341, 1265, 1159, 1092, 736, 703, 664.

LRMS (ESI+APCI) m/z $[C_{20}H_{33}N_2O_4S]^+$ ($[M+H]^+$) calculated 397.2, found 397.3.

1,1,1,3,3,3-hexafluoropropan-2-yl 7-(1-tosylpyrrolidin-2-yl)heptanoate (**3ka**)



3ka

Yield: 44%, yellow oil.

$\mathbf{R_f}$ = 0.33 (EA/Hex 1:8).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.68 (m, 2H), 7.32 – 7.28 (m, 2H), 5.77 (hept, J = 6.2 Hz, 1H), 3.62 – 3.56 (m, 1H), 3.37 (ddd, J = 10.4, 7.1, 5.1 Hz, 1H), 3.18 (dt, J = 10.4, 7.2 Hz, 1H), 2.52 (t, J = 7.5 Hz, 2H), 2.42 (s, 3H), 1.85 – 1.65 (m, 4H), 1.60 – 1.51 (m, 2H), 1.51 – 1.41 (m, 2H), 1.40 – 1.27 (m, 6H).

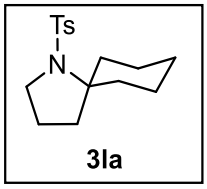
^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 143.3, 135.1, 129.7, 127.6, 120.6 (q, J = 283.31 Hz), 120.6 (q, J = 282.00 Hz), 66.4 (hept, J = 34.29 Hz), 60.6, 49.0, 36.5, 33.4, 30.8, 29.1, 28.9, 26.0, 24.6, 24.3, 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -72.47 (d, J = 6.2 Hz).

IR ($CDCl_3$, cm-1) ν 3059, 2932, 2861, 1780, 1344, 1289, 1266, 1231, 1200, 1159, 1109, 738.

LRMS (ESI+APCI) m/z $[C_{21}H_{28}F_6NO_4S]^+$ ($[M+H]^+$) calculated 504.2, found 504.1.

1-tosyl-1-azaspiro[4.5]decane (**3la**)



3la

Yield: 71%, white solid. m.p. 105 – 107 °C

R_f = 0.30 (EA/Hex 1:8).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.70 (m, 2H), 7.28 – 7.23 (m, 2H), 3.37 (t, J = 6.5 Hz, 2H), 2.40 (s, 3H), 2.37 – 2.28 (m, 2H), 1.86 – 1.81 (m, 2H), 1.78 – 1.73 (m, 2H), 1.73 – 1.65 (m, 2H), 1.62 – 1.56 (m, 1H), 1.53 – 1.46 (m, 2H), 1.28 – 1.18 (m, 3H).

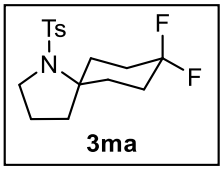
^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 139.4, 129.4, 127.2, 69.8, 49.3, 36.6, 36.6, 25.1, 24.8, 22.9, 21.6.

The spectral data are consistent with those reported in the literature[10]

IR ($CDCl_3$, cm^{-1}) ν 3057, 2932, 2864, 1452, 1329, 1265, 1152, 1095, 737, 589.

LRMS (ESI+APCI) m/z $[C_{16}H_{24}NO_2S]^+$ ($[M+H]^+$) calculated 294.1, found 294.1.

8,8-difluoro-1-tosyl-1-azaspiro[4.5]decane (**3ma**)



3ma

Yield: 40%, colorless oil.

R_f = 0.28 (EA/Hex 1:4).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.69 (m, 2H), 7.30 – 7.24 (m, 2H), 3.42 (t, *J* = 6.5 Hz, 2H), 2.71 (td, *J* = 13.7, 4.0 Hz, 2H), 2.41 (s, 3H), 2.17 – 2.05 (m, 2H), 1.95 – 1.87 (m, 2H), 1.86 – 1.80 (m, 2H), 1.79 – 1.62 (m, 2H), 1.58 – 1.48 (m, 2H).

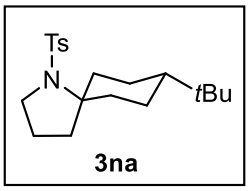
^{13}C NMR (126 MHz, $CDCl_3$) δ 143.0, 138.8, 129.6, 127.2, 122.23 (t, *J* = 241.62 Hz), 67.4, 49.4, 36.1, 32.3 (dd, *J* = 25.9, 23.6 Hz), 32.1 (d, *J* = 9.9 Hz), 22.7, 21.6.

^{19}F NMR (471 MHz, $CDCl_3$) δ -92.40 (d, *J* = 236.8 Hz), -101.74 (dtt, *J* = 236.6, 34.2, 11.1 Hz).

IR ($CDCl_3$, cm^{-1}) ν 2977, 2877, 2256, 1743, 1718, 1453, 1375, 1279, 1120, 908, 732.

LRMS (ESI+APCI) m/z $[C_{16}H_{22}F_2NO_2S]^+$ ($[M+H]^+$) calculated 330.1, found 330.1

8-(tert-butyl)-1-tosyl-1-azaspiro[4.5]decane (**3na**)



3na

Yield: 73%, white solid. m.p. 103 – 105 °C

R_f = 0.14 (EA/Hex 1:15).

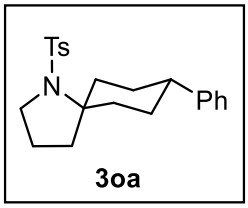
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.72 (m, 2H), 7.26 – 7.24 (m, 2H), 3.38 (t, *J* = 6.4 Hz, 2H), 2.44 – 2.29 (m, 5H), 1.85 – 1.67 (m, 6H), 1.58 – 1.49 (m, 2H), 1.17 – 1.07 (m, 1H), 1.06 – 0.94 (m, 2H), 0.83 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 139.3, 129.4, 127.2, 69.7, 49.4, 46.8, 36.8, 36.7, 32.4, 27.7, 25.5, 22.8, 21.6.

IR ($CDCl_3$, cm^{-1}) *v* 2955, 2867, 1367, 1321, 1265, 1154, 1095, 738, 656, 591, 548.

LRMS (ESI+APCI) m/z $[C_{20}H_{32}NO_2S]^+$ ($[M+H]^+$) calculated 350.2, found 350.1.

8-phenyl-1-tosyl-1-azaspiro[4.5]decane (**3oa**)



3oa

Yield: 55%, white solid. m.p. 144 – 146 °C

R_f = 0.24 (EA/Hex 1:8).

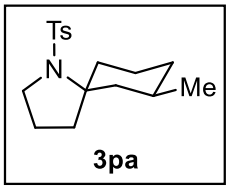
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.74 (m, 2H), 7.33 – 7.25 (m, 4H), 7.22- 7.16 (m, 3H), 3.42 (t, *J* = 6.6 Hz, 2H), 2.70 – 2.54 (m, 3H), 2.42 (s, 3H), 2.00 – 1.93 (m, 2H), 1.93 – 1.86 (m, 2H), 1.86 – 1.78 (m, 2H), 1.68 – 1.61 (m, 2H), 1.56 – 1.45 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.8, 142.6, 139.2, 129.5, 128.5, 127.2, 126.8, 126.2, 69.2, 49.3, 43.1, 36.9, 36.5, 32.4, 22.9, 21.6.

IR ($CDCl_3$, cm^{-1}) ν 3028, 3059, 2929, 2866, 1599, 1494, 1452, 1343, 1325, 1154, 1095, 736, 702, 659, 588.

LRMS (ESI+APCI) m/z $[C_{22}H_{28}NO_2S]^+$ ($[M+H]^+$) calculated 370.2, found 370.2.

7-methyl-1-tosyl-1-azaspiro[4.5]decane (**3pa**)



3pa

Yield: 60%, white solid. m.p. 71 – 73 °C

R_f = 0.17 (EA/Hex 1:15).

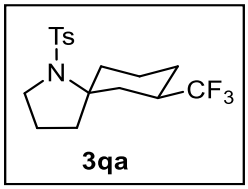
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.70 (m, 2H), 7.28 – 7.23 (m, 2H), 3.35 (t, *J* = 6.9 Hz, 2H), 2.40 (s, 3H), 2.26 (td, *J* = 13.1, 4.3 Hz, 1H), 2.03 (t, *J* = 12.3 Hz, 1H), 1.85 – 1.79 (m, 2H), 1.79 – 1.73 (m, 2H), 1.72 – 1.66 (m, 1H), 1.63 – 1.54 (m, 1H), 1.53 – 1.44 (m, 2H), 1.44 – 1.34 (m, 1H), 1.31 – 1.19 (m, 1H), 0.98 – 0.90 (m, 1H), 0.89 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 139.2, 129.4, 127.2, 70.0, 49.2, 45.3, 37.3, 35.9, 33.9, 31.2, 24.3, 23.0, 22.7, 21.6.

IR ($CDCl_3$, cm^{-1}) *v* 3056, 2952, 2925, 2867, 1598, 1455, 1330, 1265, 1152, 815, 735, 660, 592.

LRMS (ESI+APCI) m/z $[C_{17}H_{26}NO_2S]^+$ ($[M+H]^+$) calculated 308.2, found 308.2.

1-tosyl-7-(trifluoromethyl)-1-azaspiro[4.5]decane (**3qa**)



3qa

Yield: 53%, white solid. m.p. 130 – 132 °C

$\mathbf{R_f}$ = 0.25 (EA/Hex 1:8).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.69 (m, 2H), 7.30 – 7.25 (m, 2H), 3.46 – 3.31 (m, 2H), 2.48 – 2.32 (m, 5H), 2.09 – 1.98 (m, 1H), 1.91 – 1.80 (m, 3H), 1.83 – 1.71 (m, 3H), 1.74 – 1.68 (m, 1H), 1.58 – 1.50 (m, 1H), 1.41 – 1.22 (m, 2H).

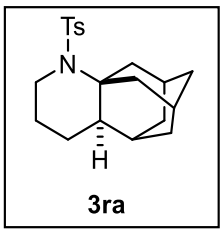
^{13}C NMR (126 MHz, $CDCl_3$) δ 143.0, 138.8, 129.6, 127.4 (q, J = 278.7 Hz), 127.2, 68.3, 49.2, 41.0 (q, J = 26.8 Hz), 37.0, 35.4, 35.1 (q, J = 2.4 Hz), 23.9 (q, J = 2.4 Hz), 22.9, 22.8, 21.6.

^{19}F NMR (471 MHz, $CDCl_3$) δ -72.5 (d, J = 8.1 Hz).

IR ($CDCl_3$, cm^{-1}) ν 2949, 2873, 1598, 1454, 1151, 1119, 1090, 1011, 679, 591, 548

LRMS (ESI+APCI) m/z $[C_{17}H_{23}F_3NO_2S]^+$ ($[M+H]^+$) calculated 362.1, found 362.2.

1-tosyldecahydrodimethanocycloocta[b]pyridine (**3ra**)



3ra

Yield: 71%, white solid. m.p. 146 – 148 °C

$\mathbf{R_f}$ = 0.24 (EA/Hex 1:15).

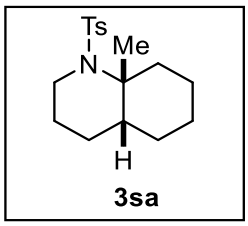
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 2H), 7.25 (d, J = 8.0 Hz, 2H), 4.13 – 4.05 (m, 1H), 3.14 (td, J = 12.8, 2.4 Hz, 1H), 2.58 (dd, J = 12.1, 3.5 Hz, 1H), 2.41 (s, 3H), 2.28 (dt, J = 12.5, 3.3 Hz, 1H), 2.05 – 1.99 (m, 1H), 1.98 – 1.92 (m, 1H), 1.82 – 1.52 (m, 12H), 1.44 – 1.33 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.4, 141.6, 129.4, 126.7, 60.6, 47.5, 42.9, 42.8, 38.1, 37.1, 35.4, 32.7, 30.6, 30.4, 30.0, 26.5, 26.4, 21.5.

IR ($CDCl_3$, cm^{-1}) v 3056, 2916, 2868, 1456, 1316, 1265, 1150, 1092, 800, 736, 665, 653, 580.

LRMS (ESI+APCI) m/z $[C_{20}H_{28}NO_2S]^+$ ($[M+H]^+$) calculated 346.2, found 346.2.

8a-methyl-1-tosyldecahydroquinoline (**3sa**)



3sa

Yield: 60%, colorless oil.

R_f = 0.24 (EA/Hex 1:15).

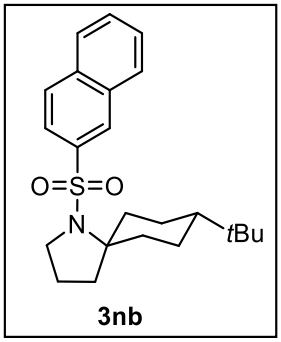
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.65 (m, 2H), 7.29 – 7.23 (m, 2H), 4.10 (dddd, J = 13.1, 4.5, 2.9, 1.2 Hz, 1H), 3.13 (td, J = 12.8, 3.3 Hz, 1H), 2.41 (s, 3H), 2.35 – 2.28 (m, 1H), 1.77 – 1.62 (m, 2H), 1.61 – 1.55 (m, 3H), 1.54 – 1.47 (m, 1H), 1.40 – 1.14 (m, 5H), 1.07 (s, 3H), 1.15 – 1.04 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 141.0, 129.4, 126.8, 63.5, 45.8, 43.8, 38.0, 30.0, 27.6, 26.4, 25.6, 23.3, 21.5, 13.7.

IR ($CDCl_3$, cm^{-1}) v 2927, 2859, 1453, 1320, 1151, 1089, 1033, 998, 904, 728, 679, 649, 582.

LRMS (ESI+APCI) m/z $[C_{17}H_{26}NO_2S]^+$ ($[M+H]^+$) calculated 308.2, found 308.1.

8-(tert-butyl)-1-(naphthalen-2-ylsulfonyl)-1-azaspiro[4.5]decane (**3nb**)



3nb

Yield: 60%, white solid. m.p. 153 – 155 °C

R_f = 0.35 (EA/Hex 1:8).

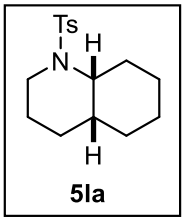
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.99 – 7.83 (m, 4H), 7.65 – 7.55 (m, 2H), 3.45 (t, *J* = 6.4 Hz, 2H), 2.44 (td, *J* = 13.1, 3.9 Hz, 2H), 1.86 – 1.70 (m, 6H), 1.63 – 1.55 (m, 2H), 1.16 (tt, *J* = 12.1, 3.1 Hz, 1H), 1.07 – 0.96 (m, 2H), 0.84 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.1, 134.6, 132.3, 129.3, 129.01, 128.5, 128.1, 127.9, 127.4, 122.9, 69.9, 49.5, 46.8, 36.8, 36.8, 32.4, 27.7, 25.5, 22.9.

IR ($CDCl_3$, cm^{-1}) *ν* 3058, 2957, 2869, 2254, 1591, 1504, 1367, 1321, 1264, 1152, 1078, 907, 732, 654.

LRMS (ESI+APCI) m/z $[C_{23}H_{32}NO_2S]^+$ ($[M+H]^+$) calculated 386.2, found 386.2.

1-tosyldecahydroquinoline (**5la**)



5la

Yield: 66%, white solid. m.p. 81 – 83 °C

R_f = 0.17 (EA/Hex 1:15).

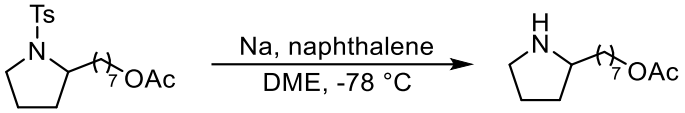
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 – 7.65 (m, 2H), 7.28 – 7.25 (m, 2H), 3.97 (dt, *J* = 12.3, 4.6 Hz, 1H), 3.74 – 3.64 (m, 1H), 2.91 (td, *J* = 13.2, 2.8 Hz, 1H), 2.41 (s, 3H), 1.79 – 1.49 (m, 7H), 1.43 – 1.19 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.8, 139.0, 129.7, 127.0, 55.4, 40.5, 35.1, 31.7, 25.7, 25.6, 24.0, 23.6, 21.7, 20.1.

IR ($CDCl_3$, cm^{-1}) ν 2930, 2863, 2255, 1598, 1329, 1171, 1150, 1091, 1008, 984, 908, 731, 660, 586.

LRMS (ESI+APCI) m/z $[C_{16}H_{24}NO_2S]^+$ ($[M+H]^+$) calculated 294.1, found 294.1.

Representative example of NTs deprotection:



3ga 85% **3ga-2**

To a solution of naphthalene (151 mg, 30 equiv) in DME (4.0 mL) at room temperature was add sodium metal (18 mg, 20 equiv). The reaction mixture was stirred for 1 h, until a dark green color solution was formed. In a 1 dr vial, NTs-pyrrolidine **3ga** (15 mg, 0.039 mmol) was dissolved in DME (0.5 mL) and cooled to -78 ºC. Na-naphthalenide solution was then added dropwise until a dark green color was persisted. The reaction mixture was stirred for 5 min at -78 ºC and then it was quenched by adding several drops of water to discharge the green color. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, concentrated under vacuum and further purified by the column chromatography (basic aluminium oxide) to give pyrrolidine **3ga-2** (7.6 mg, 85%).

R_f: 0.35 (MeOH/DCM 1:9)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.07 (t, J = 6.8 Hz, 2H), 3.03 (ddd, J = 10.4, 7.6, 5.3 Hz, 1H), 2.95 (p, J = 7.4, 6.9 Hz, 1H), 2.84 (dt, J = 10.3, 7.4 Hz, 1H), 2.07 (s, 3H), 1.94 – 1.87 (m, 2H), 1.80 – 1.70 (m, 2H), 1.66 – 1.60 (m, 2H), 1.49 – 1.23 (m, 10H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 64.6, 59.4, 46.5, 36.4, 31.9, 29.7, 29.2, 28.6, 27.4, 25.9, 25.4, 21.0.

IR ($CDCl_3$, cm^{-1}) ν 3340, 2926, 2855, 1738, 1401, 1365, 1238, 1038.

HRMS (ASAP+) m/z $[C_{13}H_{26}NO_2]$ calculated 228.1958, found 228.1968.

6. Mechanistic Studies

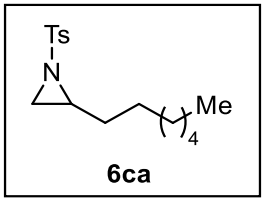
Allylic amine **6**,[11] homo allylic amine **7**,[12] deuterated alkenes (**1c-C$_1$-*d*$_2$**,[13] **1c-C$_2$-*d*$_1$**,[14] **1c-C$_3$-*d*$_2$**,[15] **1c-C$_4$-*d*$_2$**[14]) were prepared according to literature procedures.

General procedure for synthesis of aziridines (6ca, 6ca-C$_1$-*d*$_2$, 6ca-C$_2$-*d*$_1$, 6ca-C$_3$-*d*$_2$, 6ca-C$_4$-*d*$_2$)

Cesium carbonate (0.01 mmol, 0.1 equiv), **2a** (0.13 mmol, 1.3 equiv) were measured in an oven-dried 1 dram vial with a magnetic stir bar in the glovebox. In a separate vial, the deuterated alkene (0.1 mmol, 1 equiv) was dissolved in 0.35 mL of HFIP and transferred to the first vial. It was rinsed with additional 0.35

mL of HFIP and transferred again to the first vial. $[Ind^*RhCl_2]_2$ (0.0025 mmol, 2.5 mol%) in 0.3 mL of HFIP was added to the first vial and stirred at 22 °C. After 24 hours, the reaction mixture was concentrated by rotary evaporator and purified by flash chromatography using ethyl acetate and hexane as the eluent.

2-heptyl-1-tosylaziridine (**6ca**)



6ca

Yield: 95%, colorless oil.

R_f = 0.28 (EA/Hex 1:15).

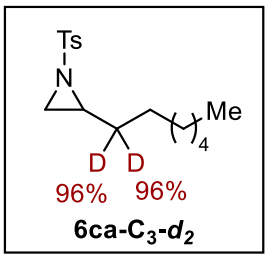
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.75 (m, 2H), 7.35 – 7.30 (m, 2H), 2.73 – 2.66 (m, 1H), 2.62 (d, *J* = 7.0 Hz, 1H), 2.43 (s, 3H), 2.05 (d, *J* = 4.6 Hz, 1H), 1.56 – 1.48 (m, 1H), 1.34 – 1.10 (m, 11H), 0.85 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.5, 135.3, 129.7, 128.1, 40.6, 33.9, 31.7, 31.4, 29.2, 29.1, 26.9, 22.7, 21.7, 14.2.

IR ($CDCl_3$, cm^{-1}) *v* 2956, 2928, 2857, 2255, 1597, 1456, 1321, 1304, 1160, 1092, 905, 814, 727, 648, 569.

LRMS (ESI+APCI) m/z $[C_{16}H_{26}NO_2S]^+$ ($[M+H]^+$) calculated 296.2, found 296.2.

2-(heptyl-1,1-d_2)-1-tosylaziridine (**6ca-C_3-d_2**)



6ca-C_3-d_2

Yield: 99%, colorless oil.

R_f = 0.28 (EA/Hex 1:15).

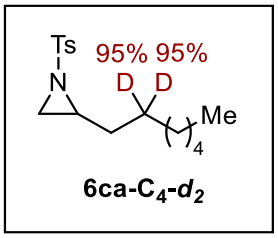
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 – 7.80 (m, 2H), 7.37 – 7.31 (m, 2H), 2.70 (dd, J = 6.9, 4.6 Hz, 1H), 2.64 (d, J = 6.9 Hz, 1H), 2.44 (s, 3H), 2.06 (d, J = 4.6 Hz, 1H), 1.30 – 1.22 (m, 2H), 1.22 – 1.14 (m, 8H), 0.87 (t, J = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.5, 135.4, 129.8, 128.1, 40.6, 33.9, 31.8, 30.7 (p, J = 19.3 Hz), 29.2, 29.1, 26.7, 22.8, 21.8, 14.2.

IR ($CDCl_3$, cm^{-1}) v 2957, 2926, 2857, 2256, 1597, 1495, 1455, 1385, 1321, 1160, 1090, 906, 813, 730.

LRMS (ESI+APCI) m/z $[C_{16}H_{24}D_2NO_2S]^+$ ($[M+H]^+$) calculated 298.2, found 298.2.

2-(heptyl-2,2-d_2)-1-tosylaziridine (**6ca-C$_4$-*d*$_2$**)



Yield: 91%, yellow oil.

R_f = 0.28 (EA/Hex 1:15).

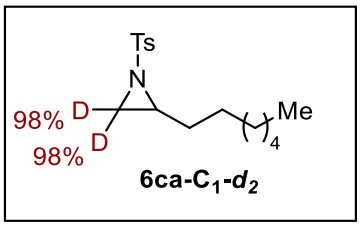
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 – 7.79 (m, 2H), 7.37 – 7.30 (m, 2H), 2.71 (m, 1H), 2.64 (d, J = 7.0 Hz, 1H), 2.44 (s, 3H), 2.05 (d, J = 4.6 Hz, 1H), 1.52 (dd, J = 14.0, 5.0 Hz, 1H), 1.34 – 1.22 (m, 3H), 1.22 – 1.13 (m, 6H), 0.86 (t, J = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.5, 135.4, 129.8, 128.1, 40.3, 33.2, 31.8, 31.3, 29.2, 28.9, 26.12 (p, J = 19.3 Hz), 22.8, 21.8, 14.2.

IR ($CDCl_3$, cm^{-1}) v 2956, 2923, 2855, 2257, 1597, 1455, 1324, 1305, 1229, 1162, 1092, 907, 815, 731, 715, 695.

LRMS (ESI+APCI) m/z $[C_{16}H_{24}D_2NO_2S]^+$ ($[M+H]^+$) calculated 298.2, found 298.2.

2-heptyl-1-tosylaziridine-3,3-d_2 (**6ca-C$_1$-*d*$_2$**)



Yield: 95%, colorless oil.

R_f = 0.28 (EA/Hex 1:15).

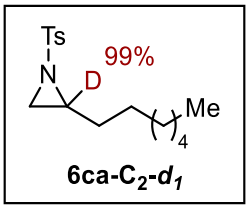
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 – 7.79 (m, 2H), 7.36 – 7.30 (m, 2H), 2.70 (dd, J = 7.6, 5.0 Hz, 1H), 2.44 (s, 3H), 1.58 – 1.49 (m, 1H), 1.37 – 1.14 (m, 11H), 0.86 (t, J = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.5, 135.4, 129.7, 128.1, 40.5, 31.8, 31.4, 29.2, 29.1, 26.9, 22.8, 21.8, 14.2.

IR ($CDCl_3$, cm^{-1}) ν 2957, 2926, 2957, 2256, 2598, 1160, 1092, 905, 730, 649, 568.

LRMS (ESI+APCI) m/z $[C_{16}H_{24}D_2NO_2S]^+$ ($[M+H]^+$) calculated 298.2, found 298.2.

2-heptyl-1-tosylaziridine-2-*d* (**6ca-C$_2$-*d$_1$***)



Yield: 95%, yellow oil.

R_f = 0.28 (EA/Hex 1:15).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.77 (m, 2H), 7.35 – 7.31 (m, 2H), 2.63 (s, 1H), 2.43 (s, 3H), 2.05 (s, 1H), 1.57 – 1.48 (m, 1H), 1.36 – 1.12 (m, 11H), 0.86 (t, J = 7.1 Hz, 3H).

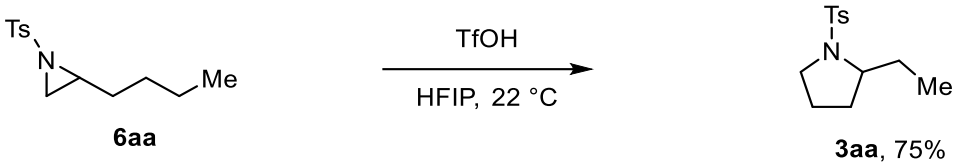
^{13}C NMR (126 MHz, $CDCl_3$) δ 144.5, 135.4, 129.7, 128.1, 40.3 (t, J = 25.6 Hz), 33.8, 31.8, 31.3, 29.2, 29.1, 26.9, 22.7, 21.7, 14.2.

IR ($CDCl_3$, cm^{-1}) ν 2932, 2860, 2257, 1454, 1321, 1162, 1051, 1032, 1015, 908, 815, 732, 648.

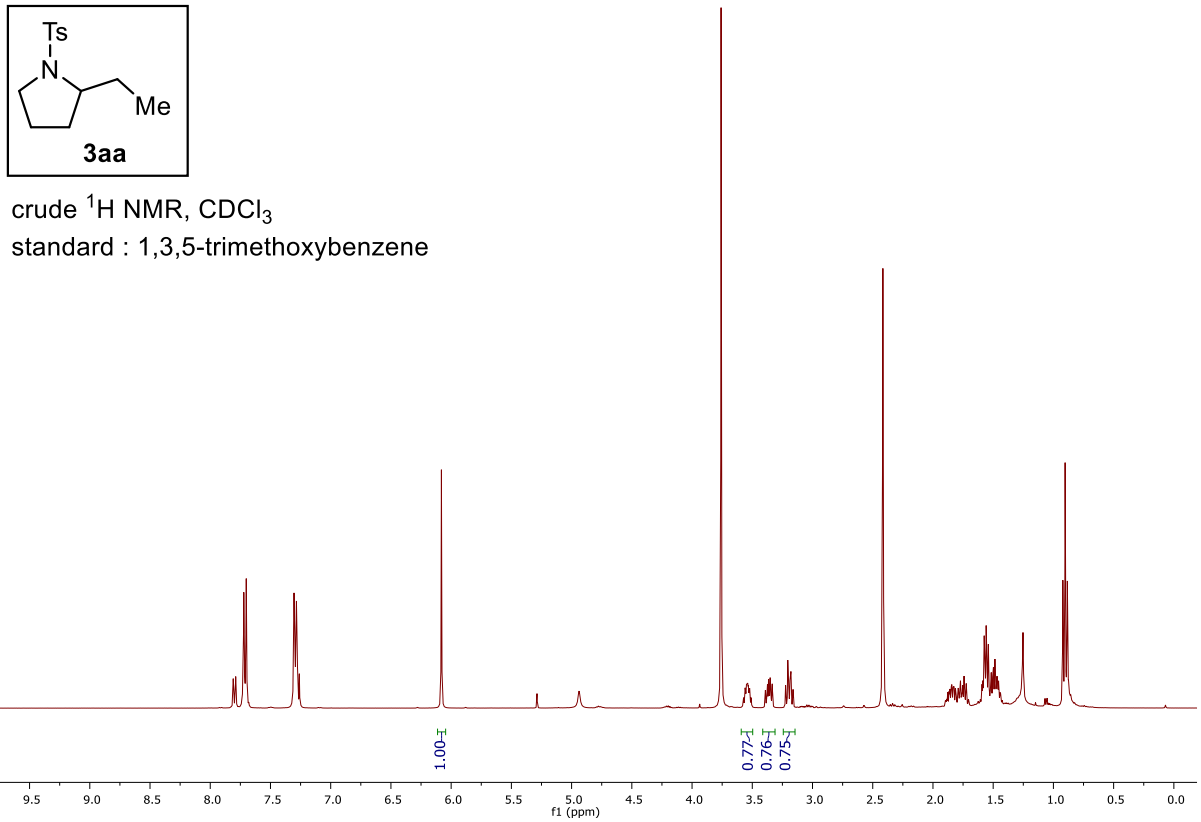
LRMS (ESI+APCI) m/z $[C_{16}H_{25}DNO_2S]^+$ ($[M+H]^+$) calculated 297.2, found 297.2.

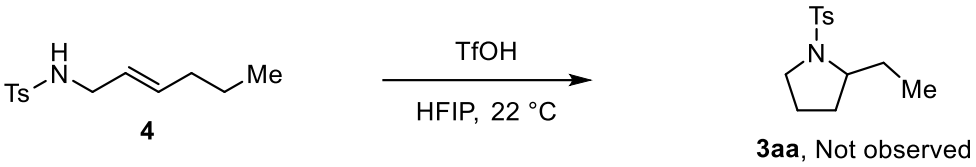
General Procedure for the Treatment of the Aziridine/Tosyl-Amide with Triflic Acid:

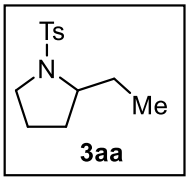
To a solution of the **aziridine/tosyl amide** (1 equiv, 0.1 mmol) in HFIP (1.0 mL), triflic acid (2 equiv, 0.2 mmol) was added and stirred at 22 °C for 24 hours. Reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ and extracted 3 times with DCM. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solid was filtered and the filtrate was concentrated by rotary evaporator. A crude ^1H NMR analysis was conducted using 1,3,5-trimethoxybenzene as the internal standard.



6aa **3aa**, 75%

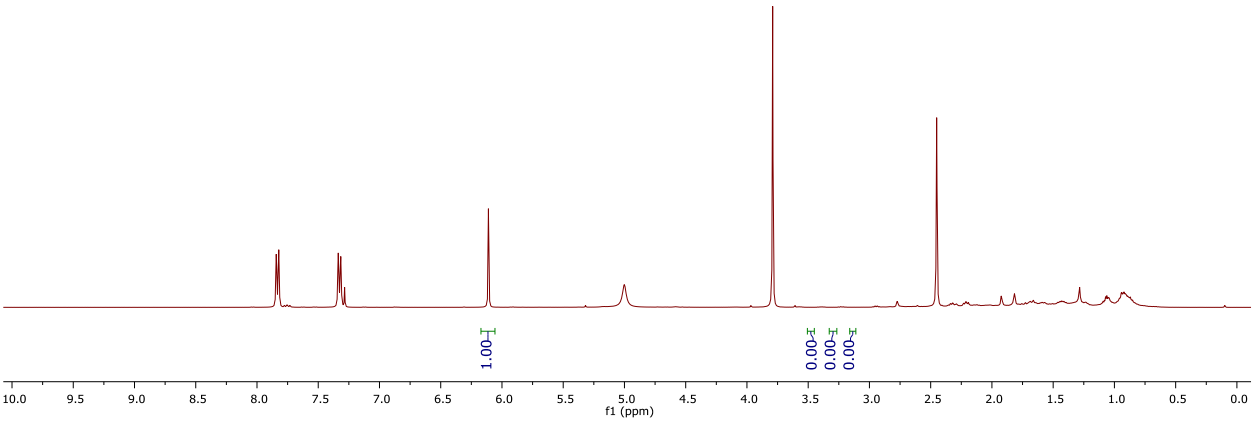


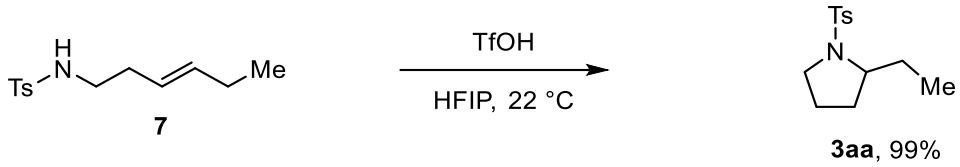


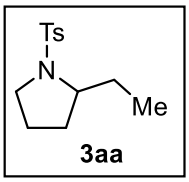


crude ^{1}H NMR, $CDCl_3$

standard : 1,3,5-trimethoxybenzene

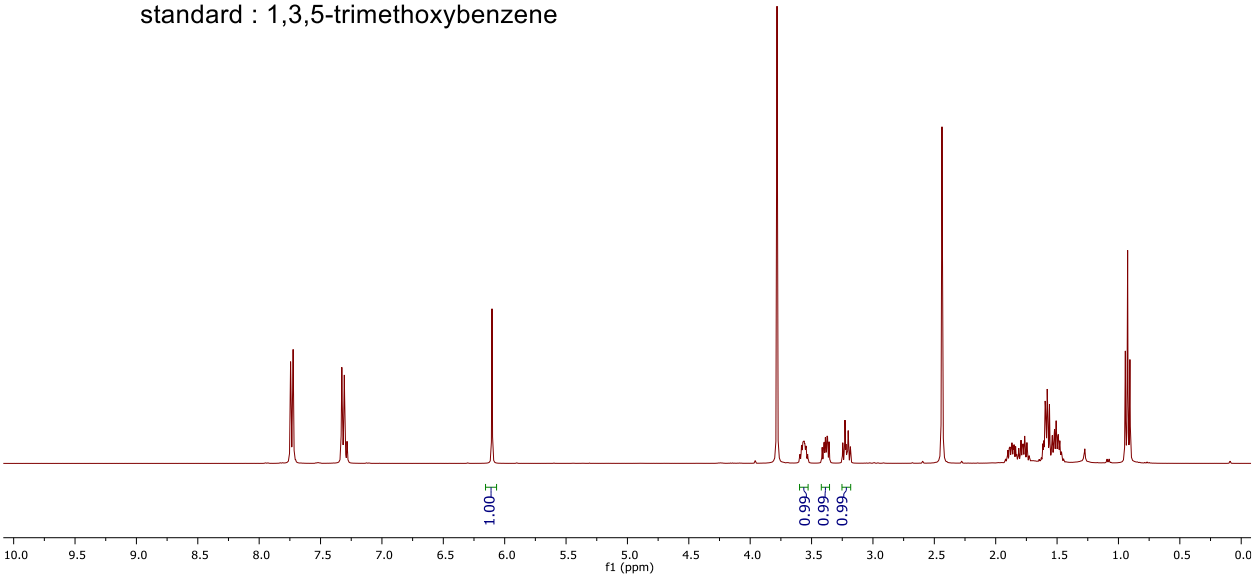


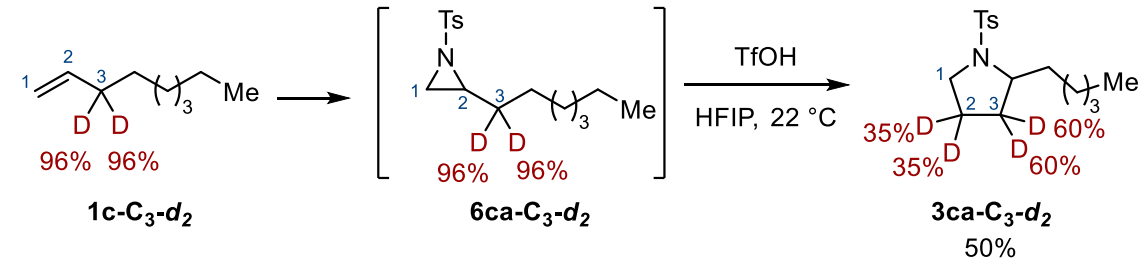




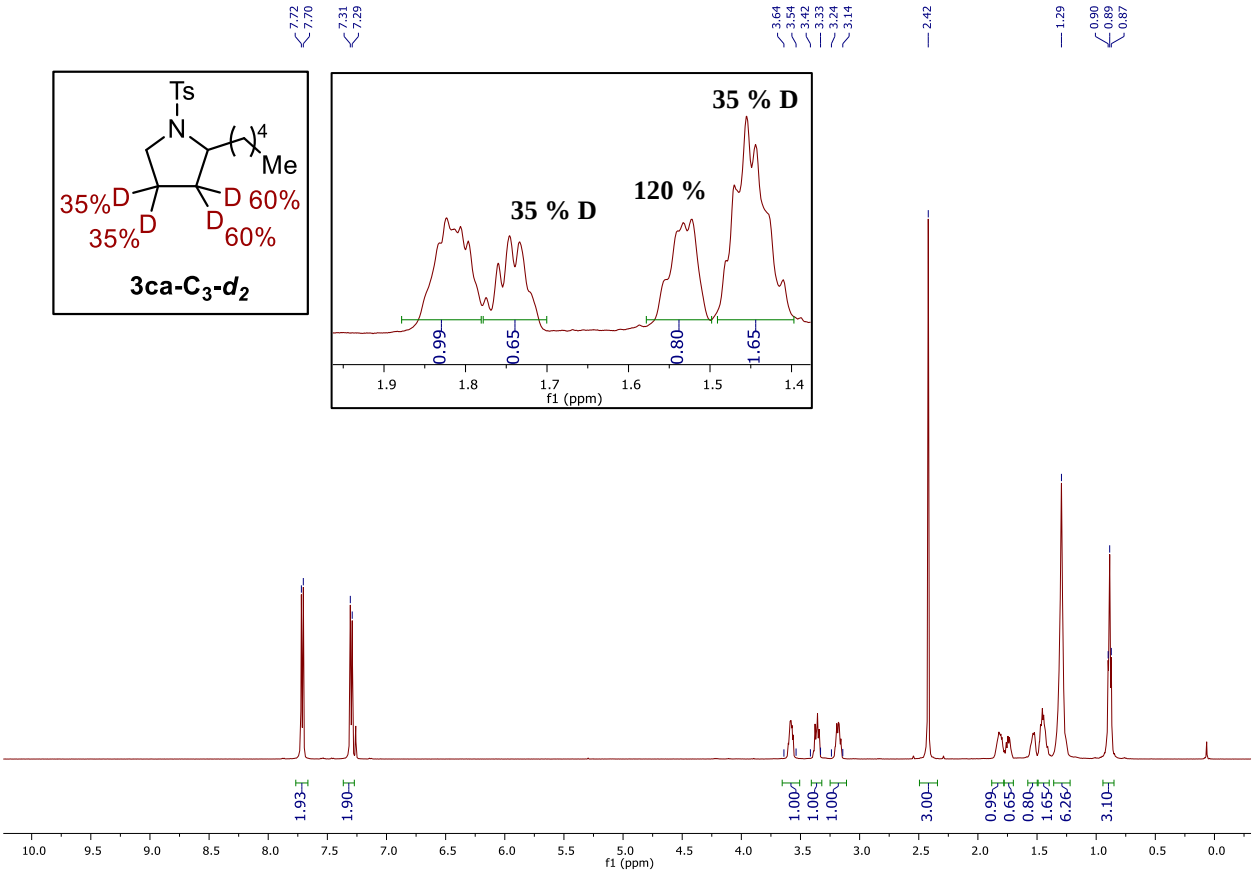
crude ^{1}H NMR, $CDCl_3$

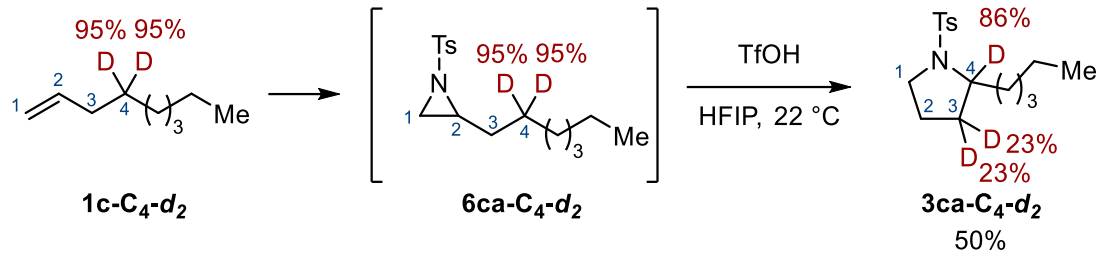
standard : 1,3,5-trimethoxybenzene

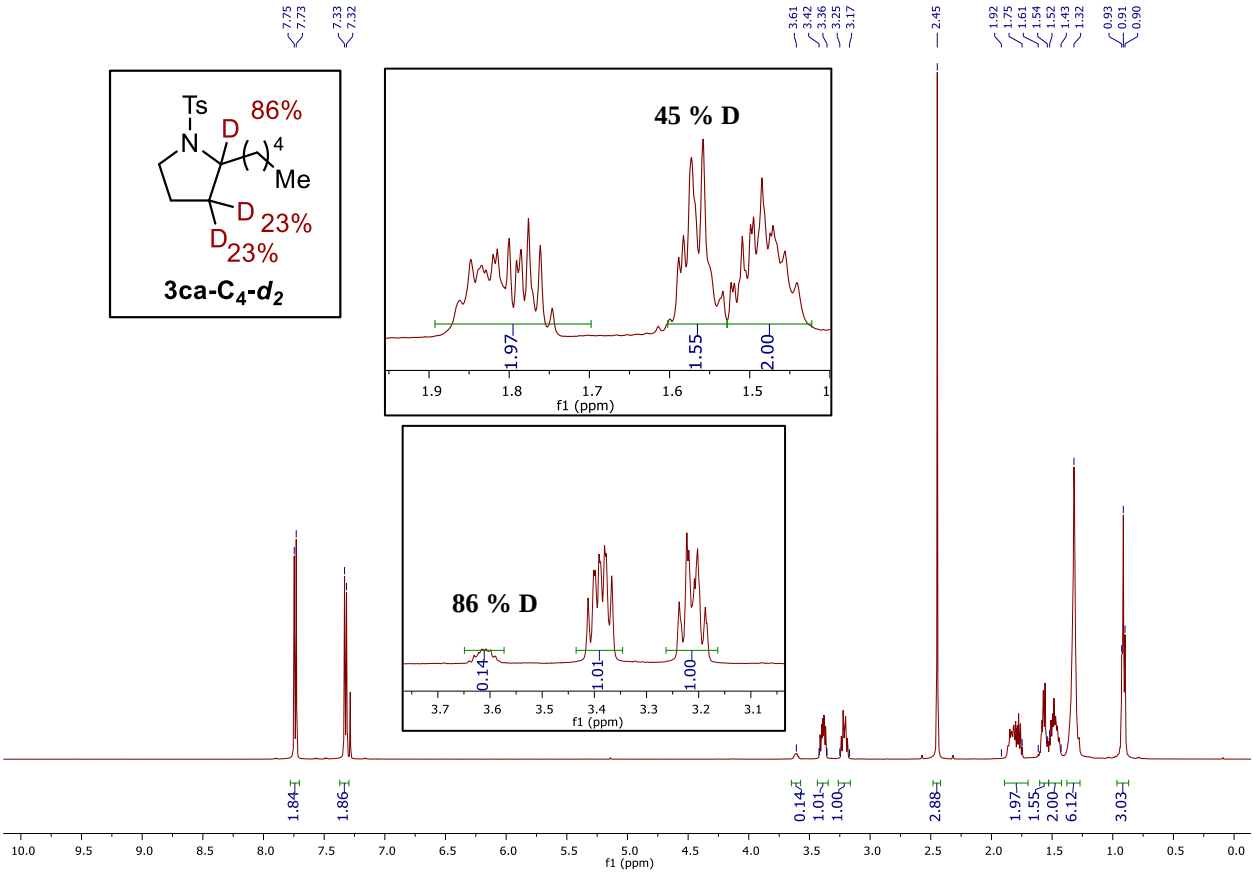


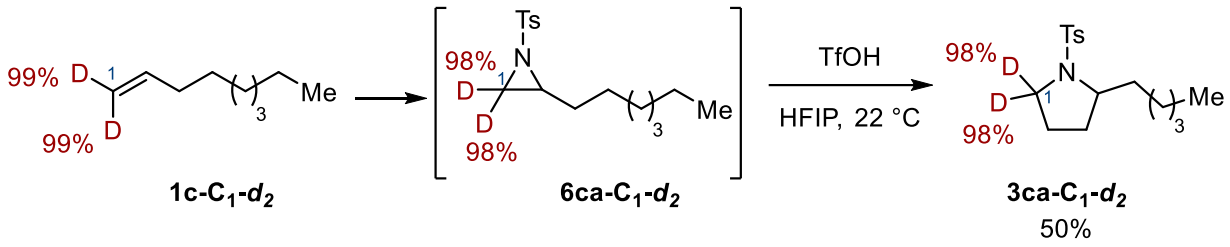


1c-C_3-d_2 **6ca-C_3-d_2** **3ca-C_3-d_2** 50%

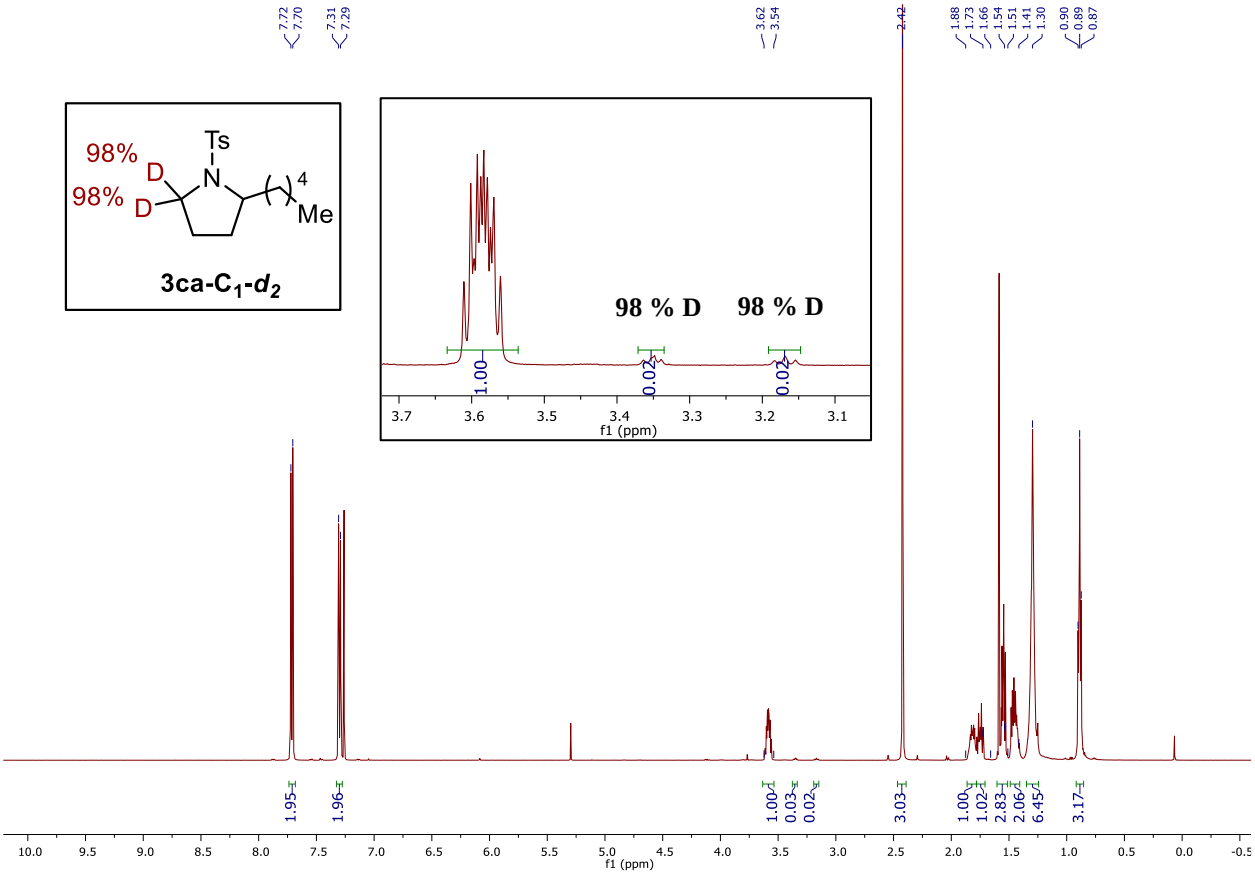


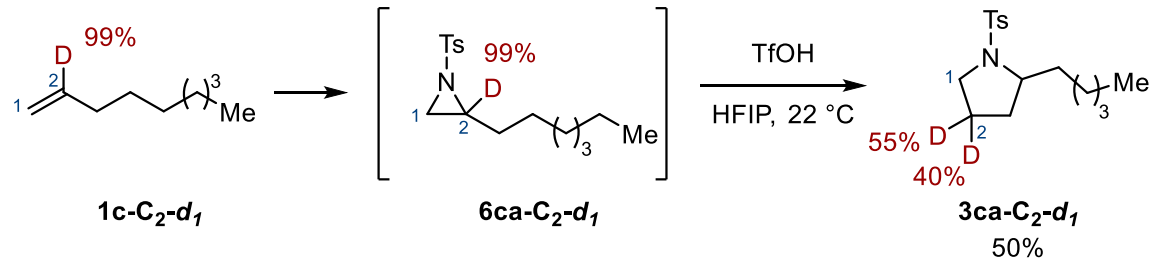

95% 95%
D D
Me
1c-C4-d2
Ts
95% 95%
D D
Me
6ca-C4-d2
TfOH
HFIP, 22 °C
Ts
86%
D
Me
D 23%
D 23%
3ca-C4-d2
50%


Ts
86%
D
Me
D 23%
D 23%
3ca-C4-d2
45 % D
86 % D
f1 (ppm)

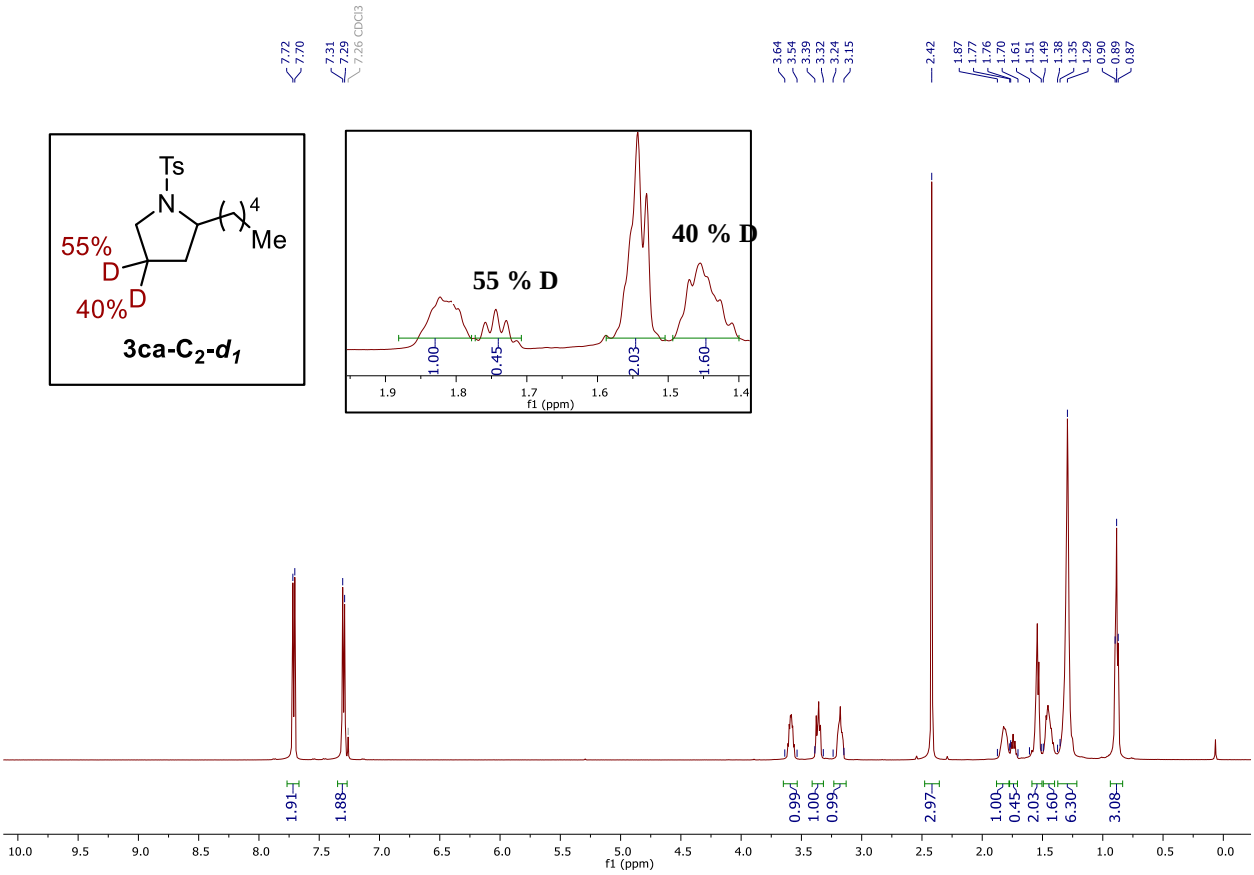


1c-C_1-d_2 **6ca-C_1-d_2** **3ca-C_1-d_2**
50%

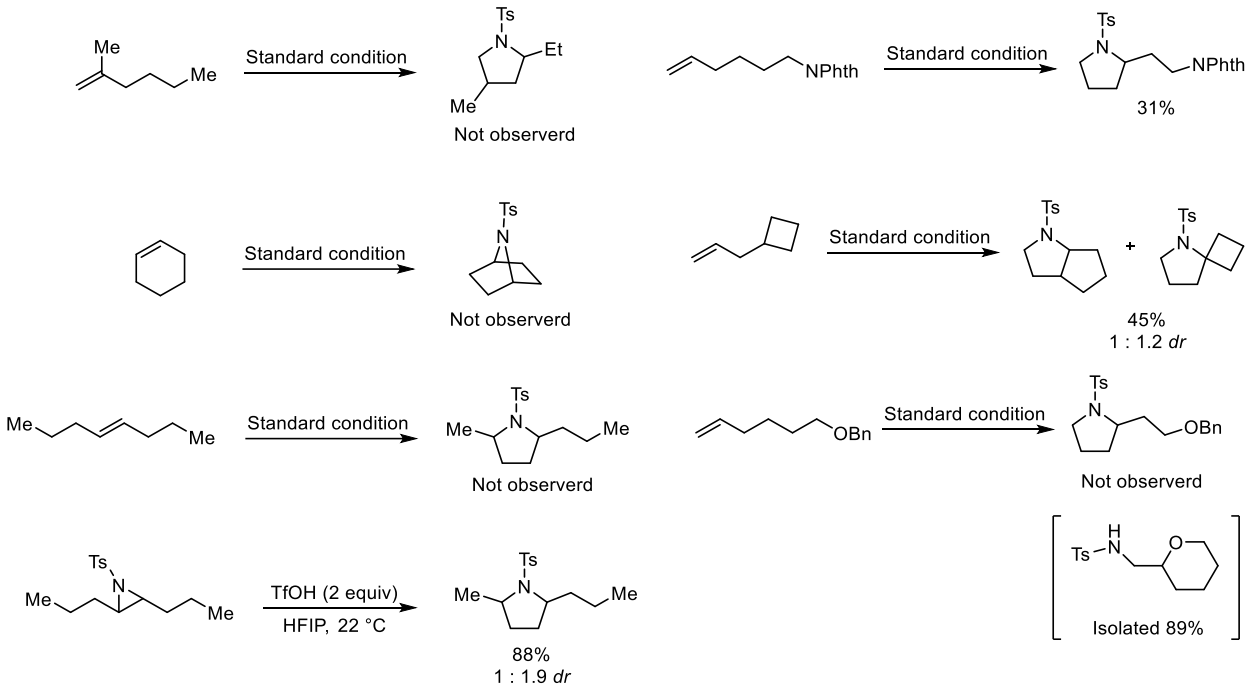




1c-C_2-d_1 **6ca-C_2-d_1** **3ca-C_2-d_1**
50%

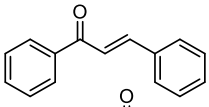
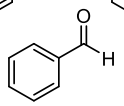
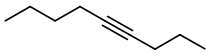
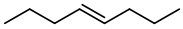
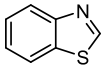
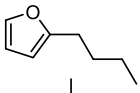
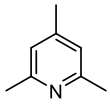
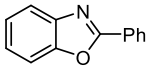
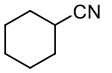


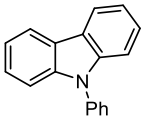
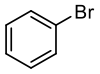
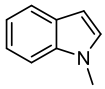
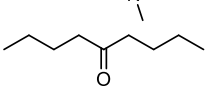
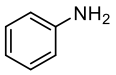
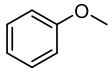
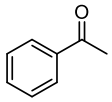
7. Limitations



8. Robustness Screening Test

A robustness screen has been conducted to evaluate the tolerance of this reaction to the given functionalities and chemical motifs, as well as the stability of these additives to the reaction conditions.[16] The standard reaction was performed using **1a** as unactivated alkene substrate in the presence of one molar equivalent of the specified additive. After the reaction, the yield of the product and the additive remaining is determined by GC-FID analysis.

Entry	Additive	Additive Remain	Yield
1		99%	43%
2		45%	45%
3		0%	40%
4		0%	14%
5		100%	0%
6		0%	12%
7		100%	55%
8		96%	25%
9		0%	10%

Entry	Additive	Additive Remain	Yield
10		50%	51%
11		24%	35%
12		100%	15%
13		41%	48%
14		100%	55%
15		100%	0%
16		61%	15%
17		100%	51%

9. X-ray Crystal Structure

Single crystal X-ray diffraction was performed at the Shared Materials Characterization Laboratory at Columbia University. Use of the SMCL was made possible by funding from Columbia University.

A chloroform solution of **3na** was diluted with pentanes by vapor diffusion, then cooled at -4 ^{o}C to afford large, colorless shards. A large fragment (.64 x .46 x .11 mm) was separated carefully, mounted on a Mitegen mount with Paratone oil, and cooled to 100 K on the diffractometer. Complete data (99.5%) were collected to 0.8 Å using Mo radiation. 16080 reflections were collected (4620 unique, 3470 observed) with R(int) 5.9% and R(sigma) 6.6% after Gaussian absorption and beam profile correction (largest correction factor 1.49).

The space group was assigned as Pbca based on the systematic absences. The structure solved readily using ShelXT with 1 molecule in the asymmetric unit. All non-H atoms were located in the initial solution and refined anisotropically with no restraints. C-H hydrogens were placed in calculated positions and refined with riding coordinates and ADPs; the hydrogens of the aryl-CH_3 group were disordered over two positions in a 57:43 ratio.

The final refinement (4620 data, 0 restraints, 222 parameters) converged with R_1 ($F_o > 4\sigma(F_o)$) = 5.4%, wR_2 = 11.7%, S = 1.05. The largest Fourier features were 0.28 and -0.36 e^- A^{-3}.

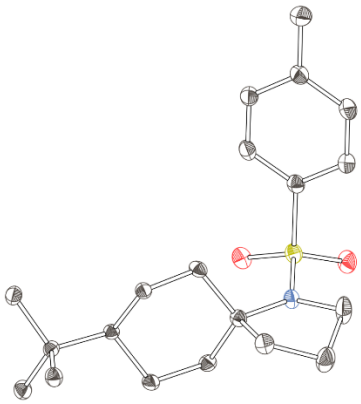


Figure S1. Molecular structure of **3na**. Black, carbon; blue, nitrogen; red, oxygen; yellow, sulfur. Hydrogen atoms are omitted for clarity.

A chloroform solution of **3pa** was diluted with pentane by vapor diffusion to afford a jumble of flaky colorless blocks. With difficulty, a single-crystalline fragment (.27 x .14 x .05 mm) was separated carefully, mounted on a glass fiber with Paratone oil, and cooled to 100 K on the diffractometer. Complete data were collected to 0.8 Å. 18219 reflections were collected (5874 unique, 5812 observed) with R(int) 4.5% and R(sigma) 4.6% after analytical absorption correction (maximum correction factor 1.23).

Based on the systematic absences, the space group was Cc or C2/c. Using ShelXT, the structure solved readily in Cc with 2 molecules in the asymmetric unit. The space group was correct because the Flack parameter was near 0 and no (pseudo-)symmetry was detected by Platon. All non-H atoms were located in the initial solution and refined anisotropically with no restraints. C-H hydrogens were placed in calculated positions and refined with riding coordinates and ADPs.

The final refinement (5874 data, 2 restraints, 383 parameters) converged with R_1 ($F_o > 4\sigma(F_o)$) = 4.6%, wR_2 = 11.9%, S = 1.05. The largest Fourier features were 0.40 and -0.39 e^- A^{-3}. The Flack parameter was 0.011(12).

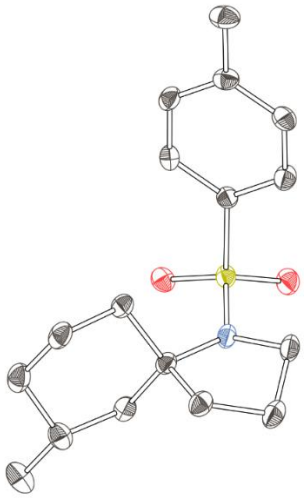


Figure S2. Molecular structure of **3pa**. Both independent molecules are shown but their relative orientation is arbitrary.

A benzene solution of **3ra** was diluted with pentane by vapor diffusion to afford large, colorless blocks. Part of a crystal (.67 x .52 x .23 mm) was separated carefully, mounted with Paratone oil, and cooled to 100 K on the diffractometer. The crystal was a triclinic, nonmerohedral twin with a twofold rotation around the reciprocal axis 010 as the twin law. Complete data were collected to 0.8 Å resolution. The second twin component was somewhat weaker and its isolated reflections were omitted; the data set contained 6772 overlapped reflections and 6803 isolated reflections for the first component. R(int) was 5.3% and R(sigma) 11.7% after Gaussian absorption correction and beam profile correction (max. correction factor 3.9).

The structure solved readily in P-1 with two molecules in the asymmetric unit. Subsequent refinement was against the twinned data (HKLF 5 format). C-H hydrogens were placed in calculated positions and refined with riding coordinates and ADPs.

The final refinement (8426 data, 0 restraints, 436 parameters) converged with R_1 ($F_o > 4\sigma(F_o)$) = 6.0%, wR_2 = 11.2%, S = 1.04. The largest Fourier features were 0.74 and -0.53 e^- A^{-3}.

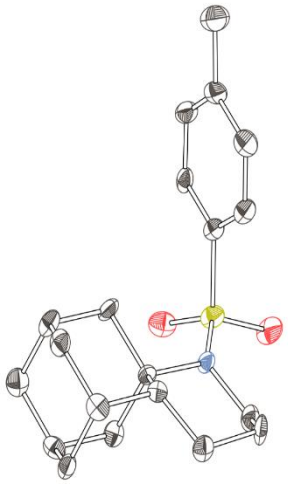


Figure S3. Molecular structure of **3ra**. One of the two independent molecules is shown. Black, carbon; blue, nitrogen; red, oxygen; yellow, sulfur. Hydrogen atoms are omitted for clarity.

A benzene solution of **5la** was diluted with pentane by vapor diffusion and cooled at -4 deg. C to afford one large, irregular block. A fragment (.68 x .32 x .21 mm) was separated carefully, mounted on Mitegen loop with Paratone oil, and cooled to 100 K on the diffractometer. Complete data were collected to 0.8 Å. 29503 reflections were collected (3926 unique, 3379 observed) with R(int) 5.8% and R(sigma) 3.7% after Gaussian absorption and beam profile correction (maximum correction factor 2.58). The space group was assigned as P4 2 /n based on the systematic absences and confirmed by solution in ShelXT. The structure solved readily with all non-H atoms located in the initial solution and refined anisotropically with no restraints. C-H hydrogens were placed in calculated positions and refined with riding coordinates and ADPs.

The final refinement (3926 data, 0 restraints, 182 parameters) converged with R_1 ($F_o > 4\sigma(F_o)$) = 5.0%, wR_2 = 11.3%, S = 1.12. The largest Fourier features were 0.33 and -0.40 e^- A^{-3}.

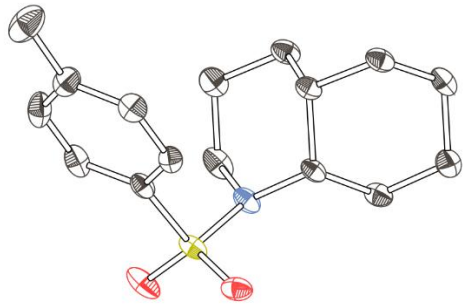


Figure S4. Molecular structure of **5la**. One of the two independent molecules is shown. Black, carbon; blue, nitrogen; red, oxygen; yellow, sulfur. Hydrogen atoms are omitted for clarity.

Compound	3na	3pa	3ra	5la
Formula	$C_{20}H_{31}NO_2S$	$C_{20}H_{27}NO_2S$	$C_{17}H_{25}NO_2S$	$C_{16}H_{23}NO_2S$
MW	349.52	345.48	307.44	293.41
Space group	Pbca	P-1	Cc	$P4_2/n$
a (Å)	9.7111(4)	6.4929(6)	11.6792(2)	15.6435(2)
b (Å)	11.8859(6)	10.1262(15)	11.2211(2)	15.6435(2)
c (Å)	33.1687(11)	26.330(2)	24.8608(4)	12.4533(3)
α (°)	90	89.500(11)	90	90
β (°)	90	84.004(7)	99.2204(16)	90
γ (°)	90	88.445(11)	90	90
V (Å^3)	3828.5(3)	1721.0(3)	3215.98(10)	3047.56(11)
Z	8	4	8	8
ρ_{calc} (g cm^{-3})	1.213	1.333	1.27	1.279
T (K)	100	100	100	100
λ (Å)	0.71073	0.71073	1.54184	0.71073
$2\theta_{min}$, $2\theta_{max}$	7, 59	7, 59	7, 146	7, 59
Nref	16080	13575	18219	29503
R(int), R(σ)	.0592, .0665	.053, .137	.0448, .0464	.0578, .0374
μ(mm^{-1})	0.181	0.201	1.815	0.214
Size (mm)	.64 x .46 x .11	.67 x .52 x .23	.27 x .14 x .05	.68 x .32 x .21
T_{max} / T_{min}	1.48	3.9	1.23	2.58
Data	4620	8426	5874	3926
Restraints	0	0	2	0
Parameters	222	436	383	182
R_1(obs)	0.0543	0.0601	0.0457	0.0502
wR_2(all)	0.1172	0.1116	0.1187	0.1128
S	1.050	1.043	1.053	1.125
Peak, hole (e$^-$ Å^{-3})	0.28, -0.36	0.74, -0.53	0.40, -0.39	0.33, -0.40
Flack			0.011(12)	

10. References

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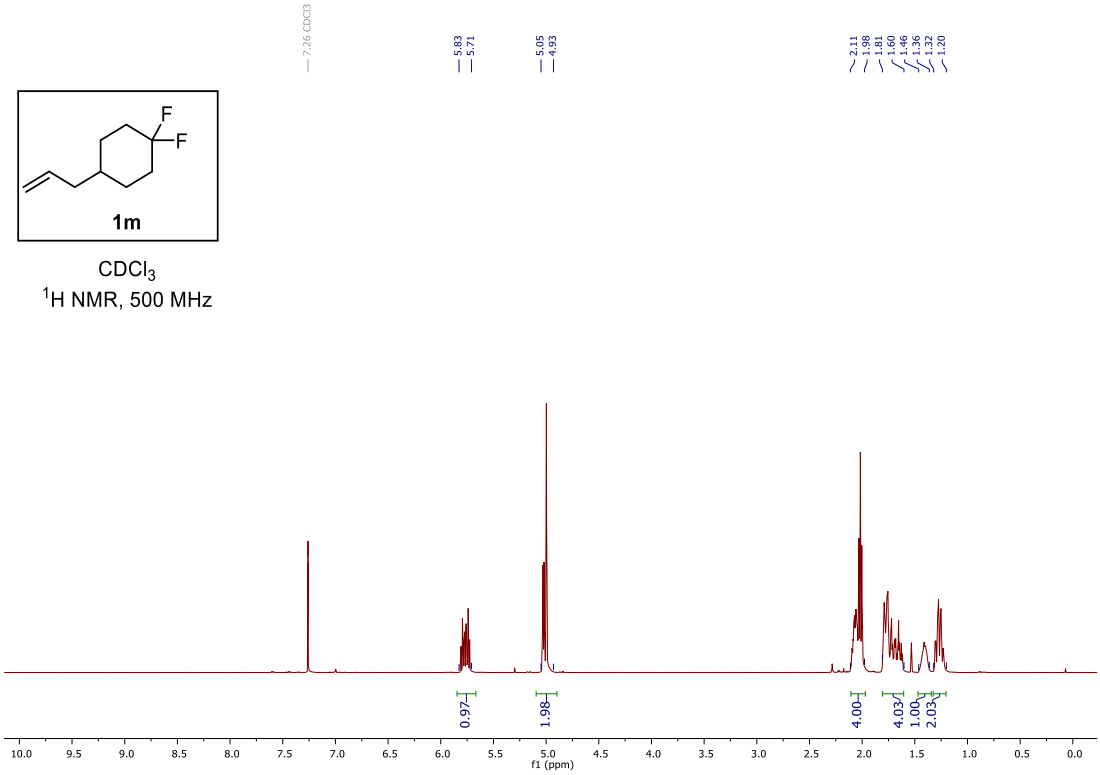
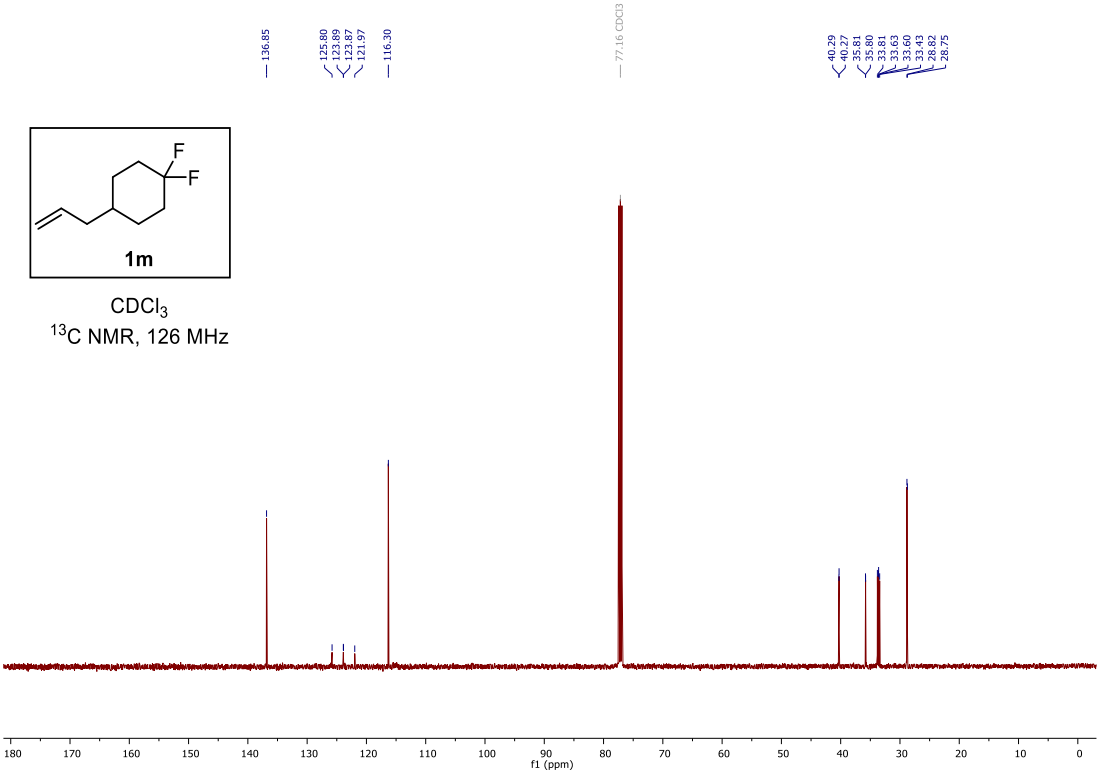
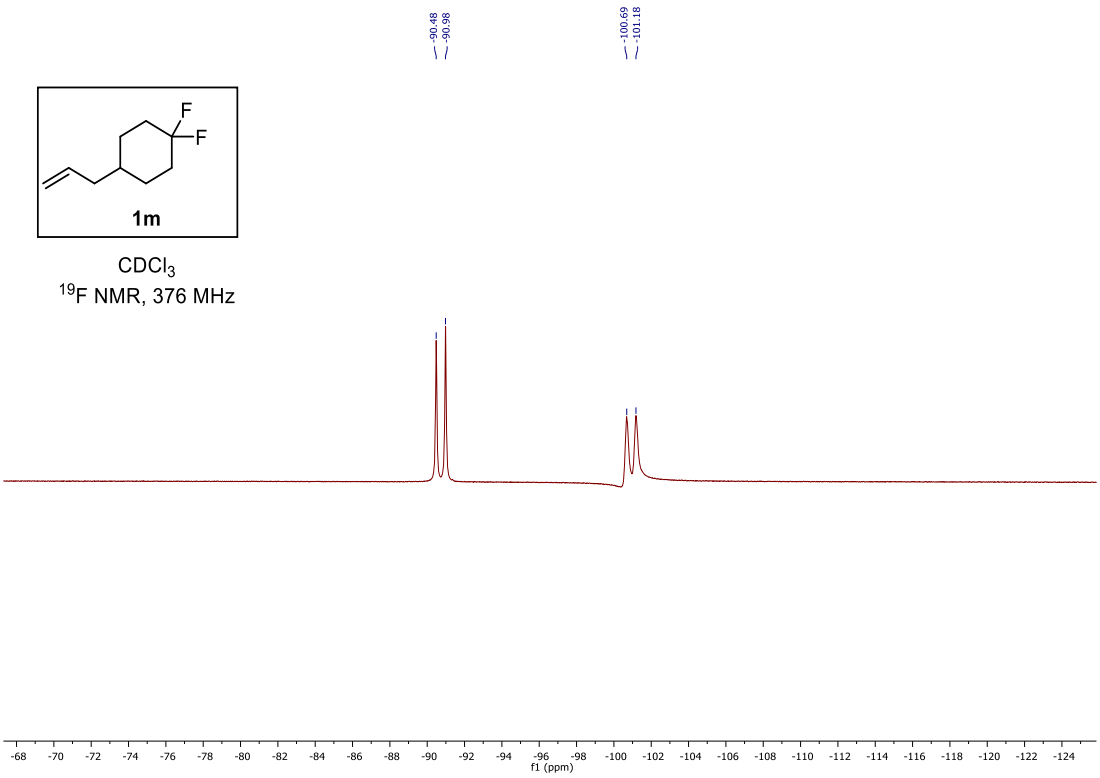
11. NMR Spectra

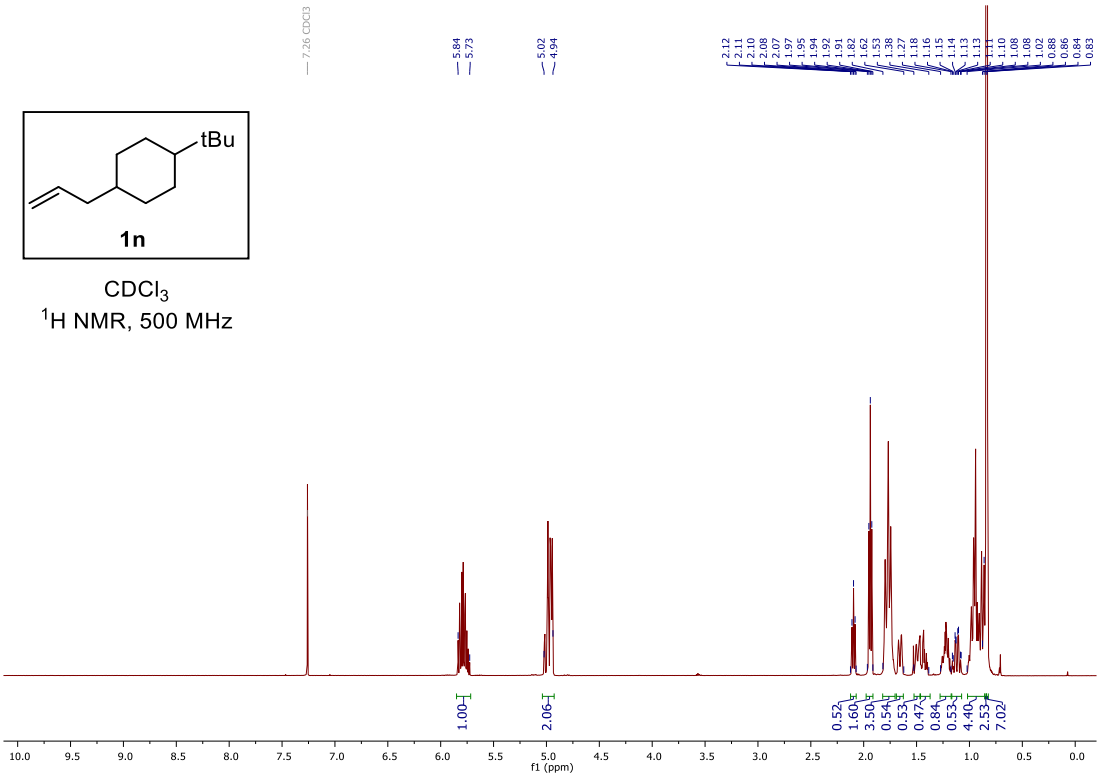
$CDCl_3$
^{1}H NMR, 500 MHz

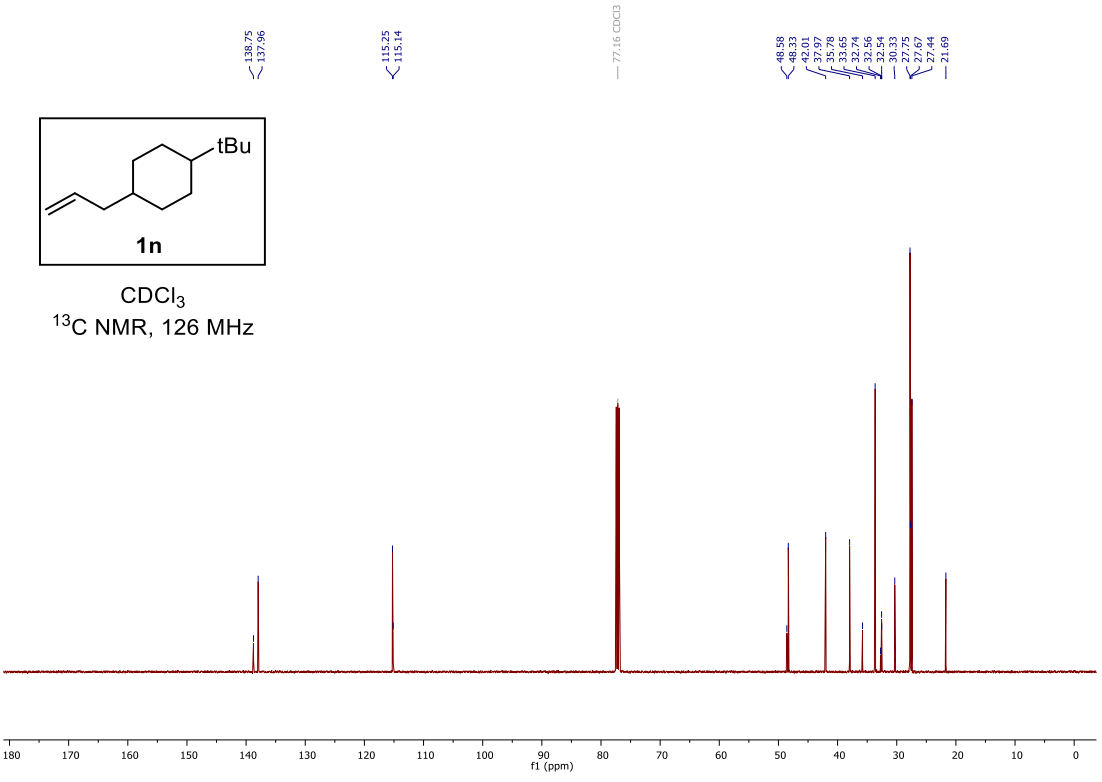


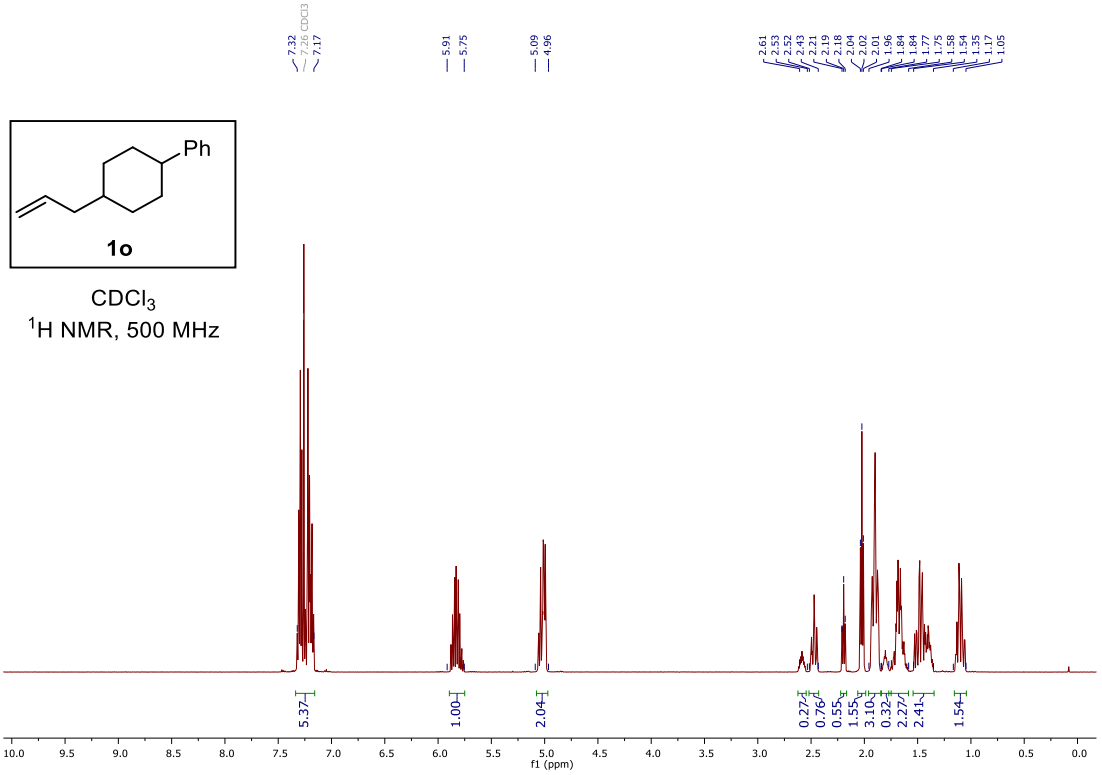
$CDCl_3$
^{13}C NMR, 126 MHz

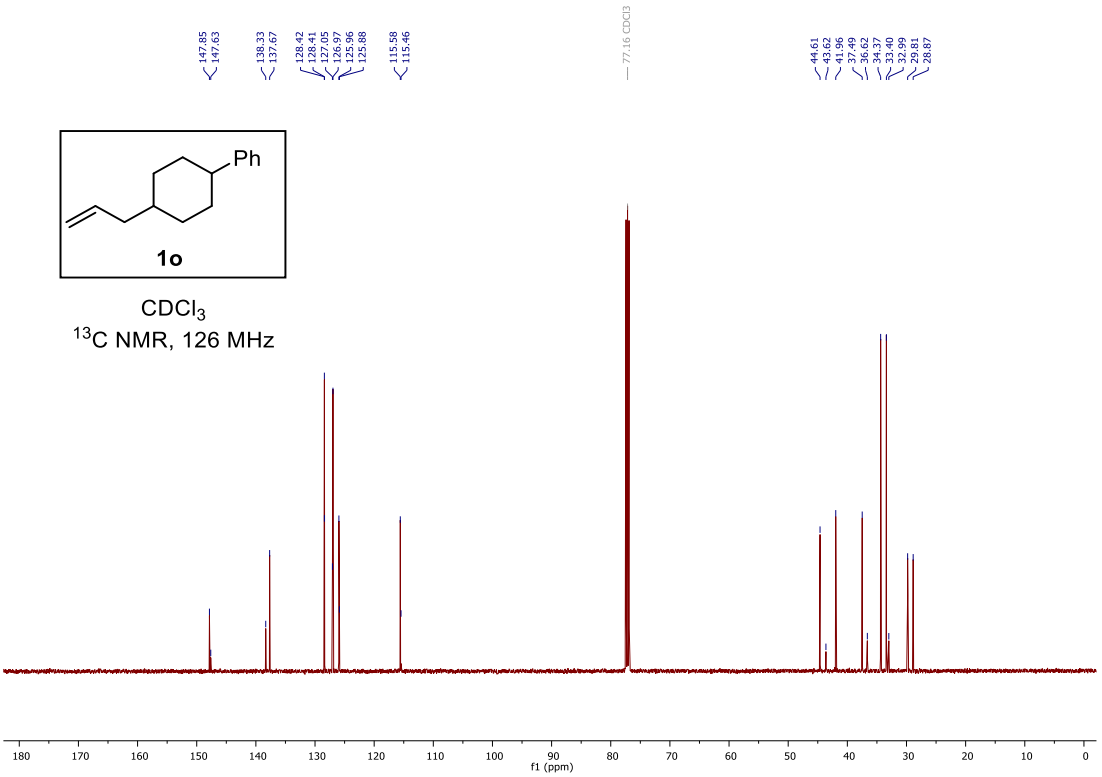



-90.48
-90.98
-100.69
-101.18
F
F
1m
CDCl3
19F NMR, 376 MHz
-68 -70 -72 -74 -76 -78 -80 -82 -84 -86 -88 -90 -92 -94 -96 -98 -100 -102 -104 -106 -108 -110 -112 -114 -116 -118 -120 -122 -124
f1 (ppm)

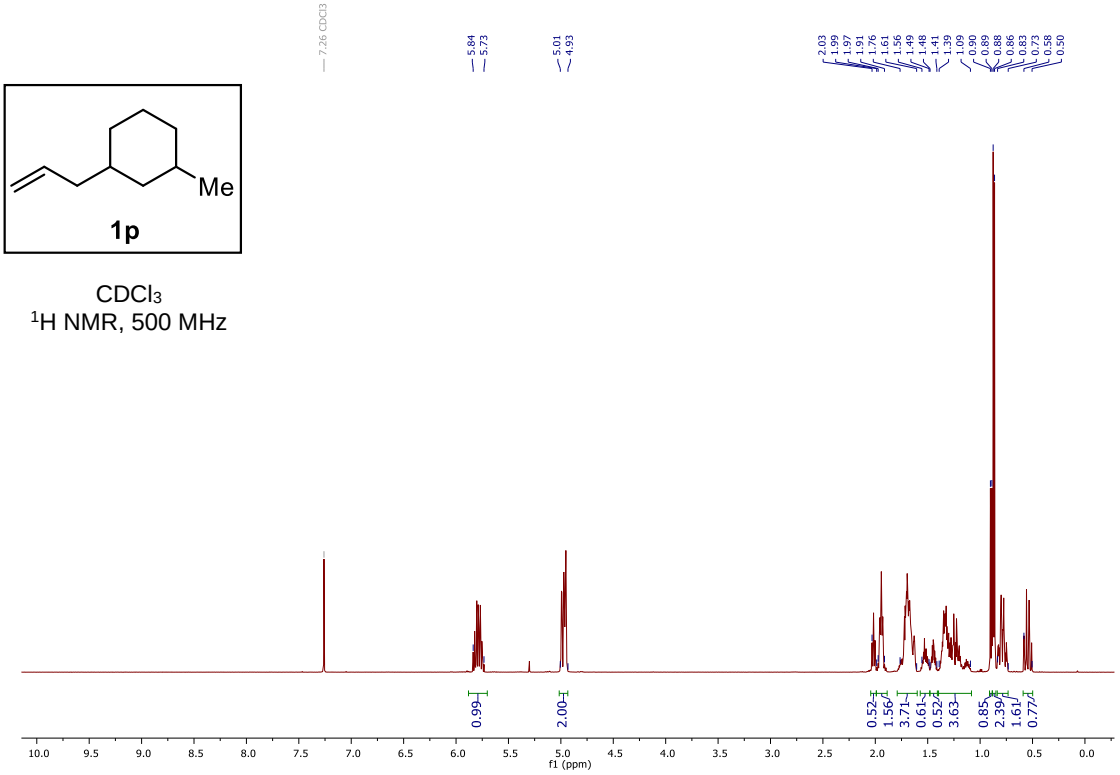

tBu
1n
CDCl3
1H NMR, 500 MHz
7.26 CDCl3
5.84
5.73
5.02
4.94
2.12
2.11
2.10
2.08
2.07
1.97
1.95
1.94
1.92
1.91
1.82
1.62
1.53
1.38
1.27
1.18
1.16
1.15
1.14
1.13
1.11
1.10
1.08
1.08
1.02
0.88
0.86
0.84
0.83
1.00
2.06
0.52
1.60
3.50
0.54
0.53
0.47
0.84
0.53
4.40
2.53
7.02
f1 (ppm)


tBu
1n
CDCl3
13C NMR, 126 MHz
138.75
137.96
115.25
115.14
77.16 CDCl3
48.58
48.33
42.01
37.97
35.78
33.65
32.74
32.56
32.54
30.33
27.75
27.67
27.44
21.69
f1 (ppm)

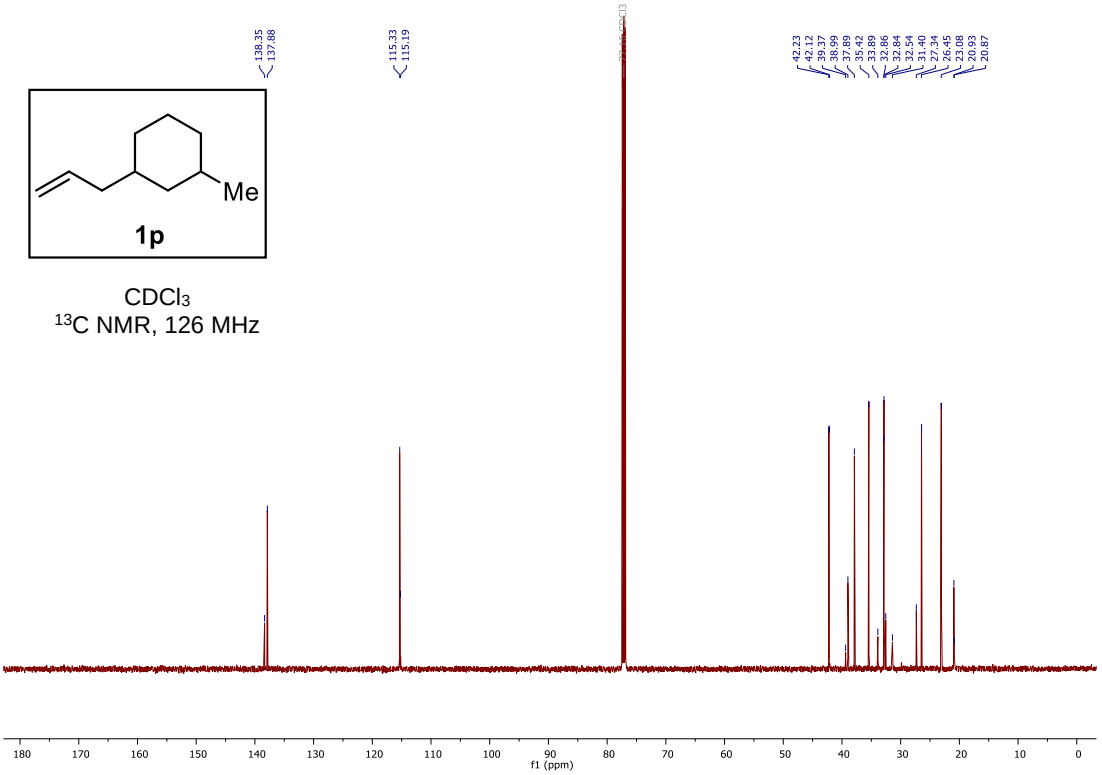

Ph
1o
CDCl3
1H NMR, 500 MHz
f1 (ppm)


Ph
1o
CDCl3
13C NMR, 126 MHz
f1 (ppm)

$CDCl_3$
^1H NMR, 500 MHz

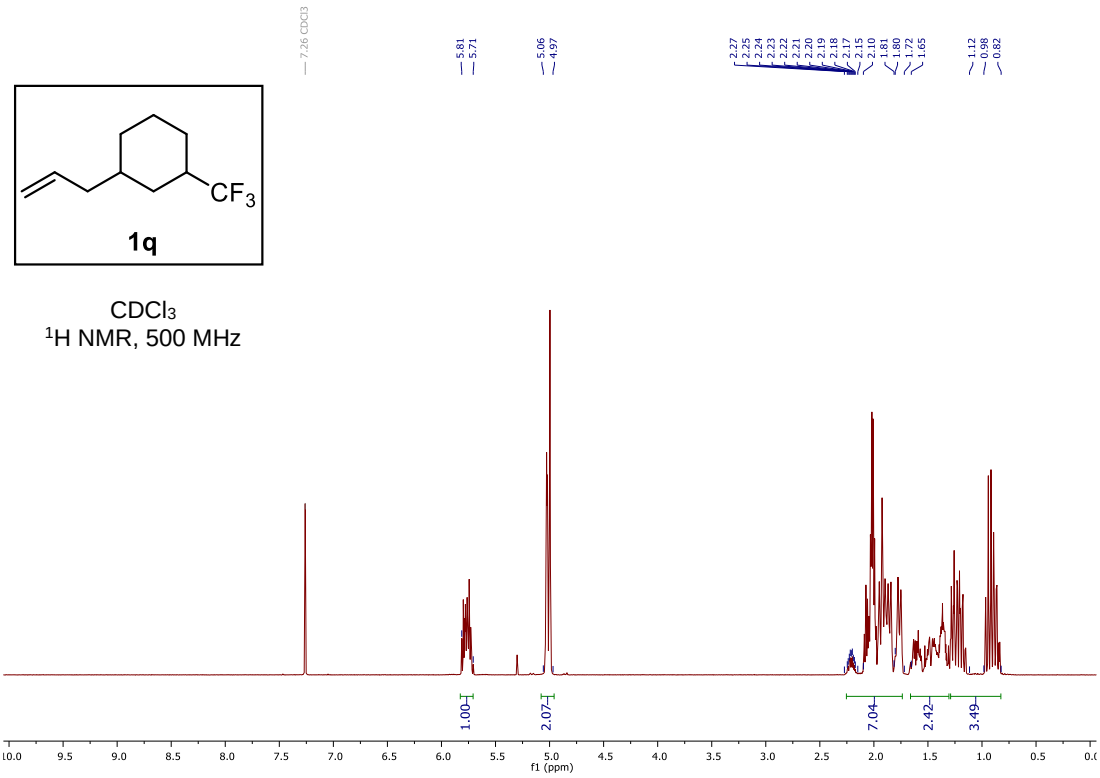


$CDCl_3$
^{13}C NMR, 126 MHz



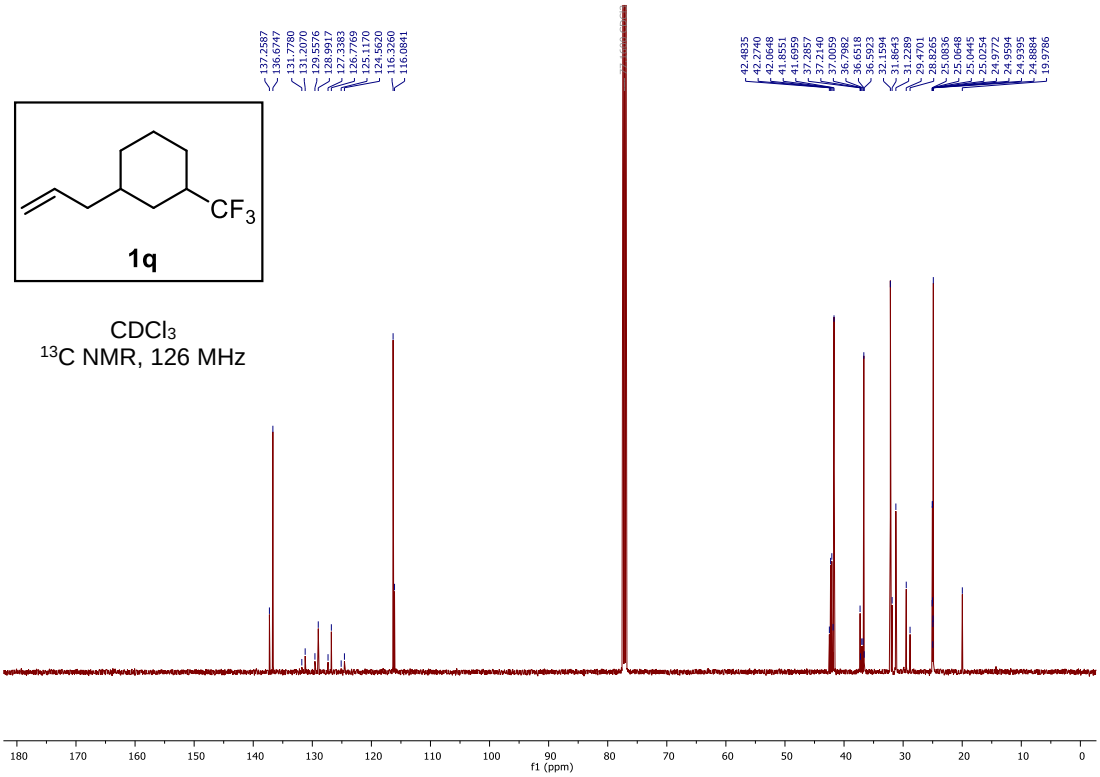
1q

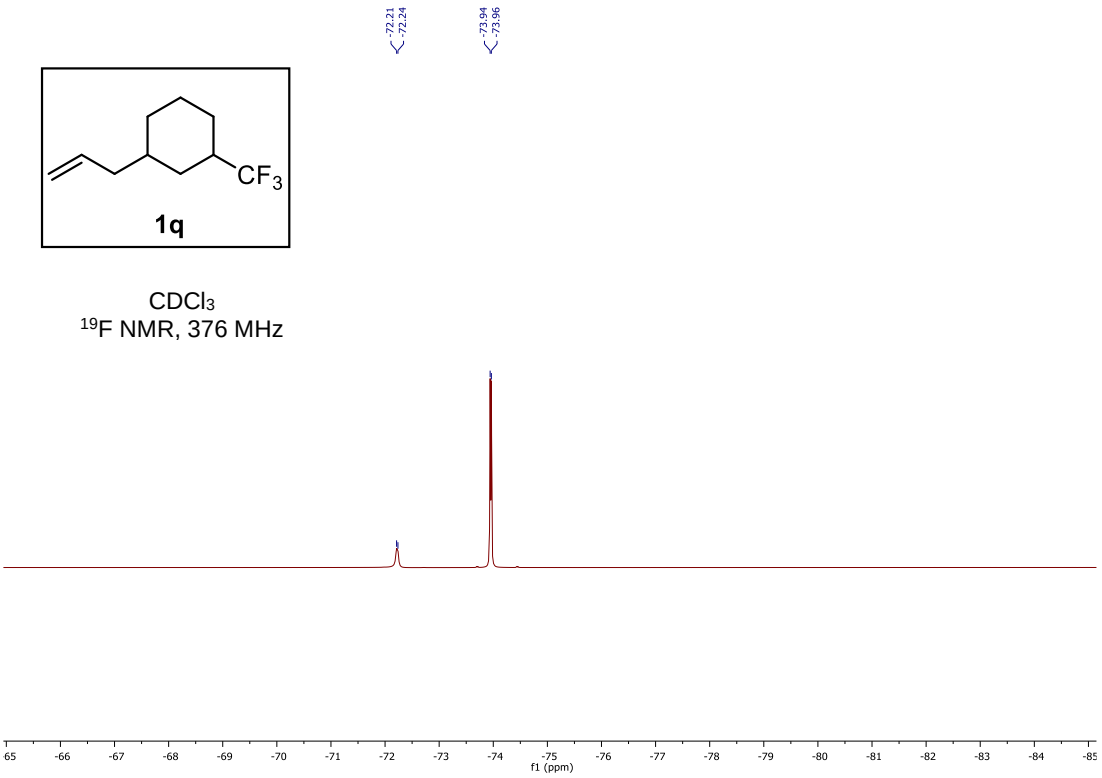
$CDCl_3$
^{1}H NMR, 500 MHz



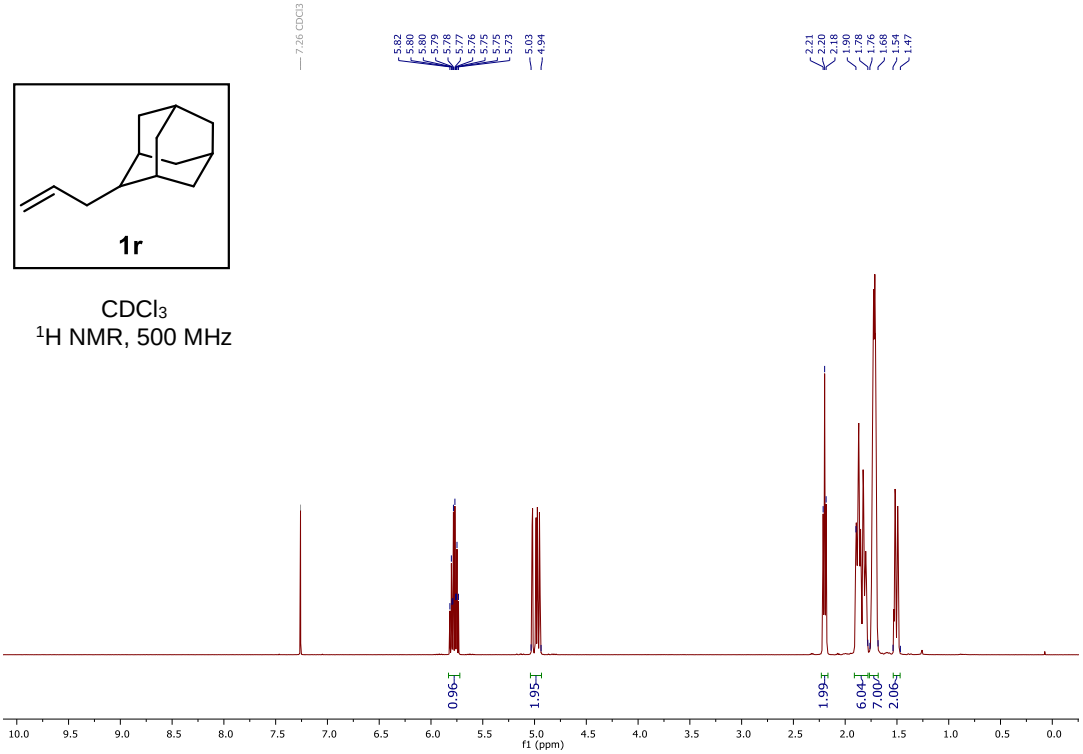
1q

$CDCl_3$
^{13}C NMR, 126 MHz

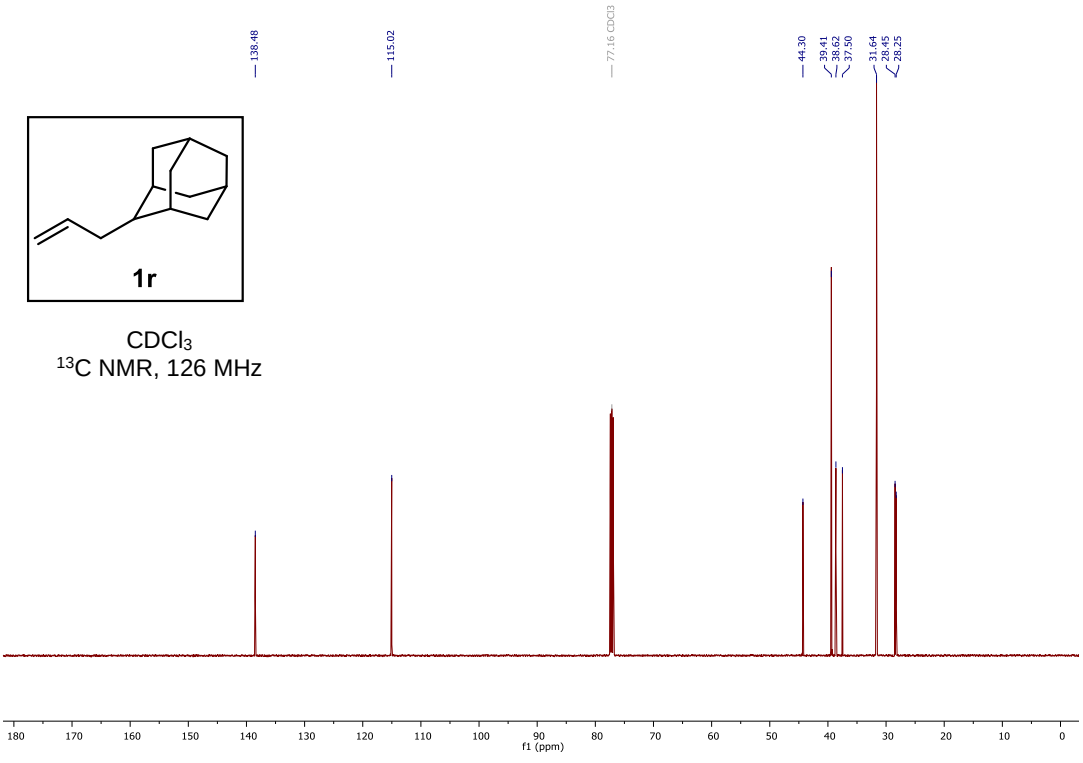



-72.21
-72.24
-73.94
-73.96
CF3
1q
CDCl3
19F NMR, 376 MHz
65
-66
-67
-68
-69
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79
-80
-81
-82
-83
-84
-85
f1 (ppm)

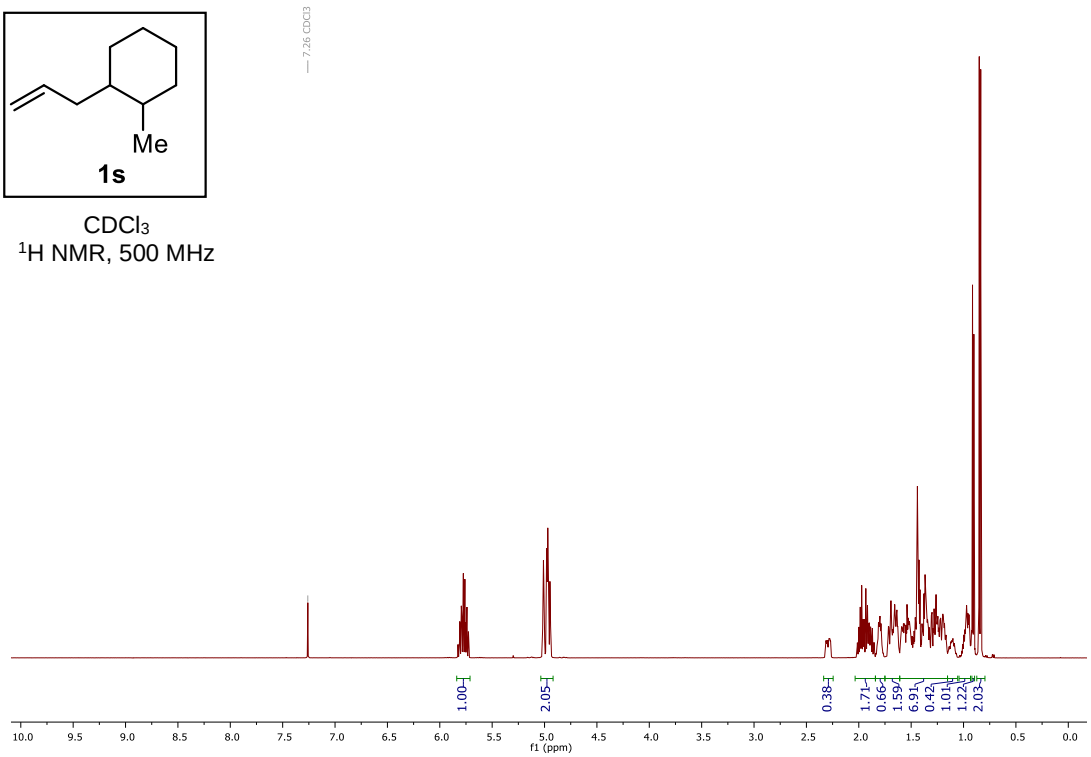
$CDCl_3$
^{1}H NMR, 500 MHz



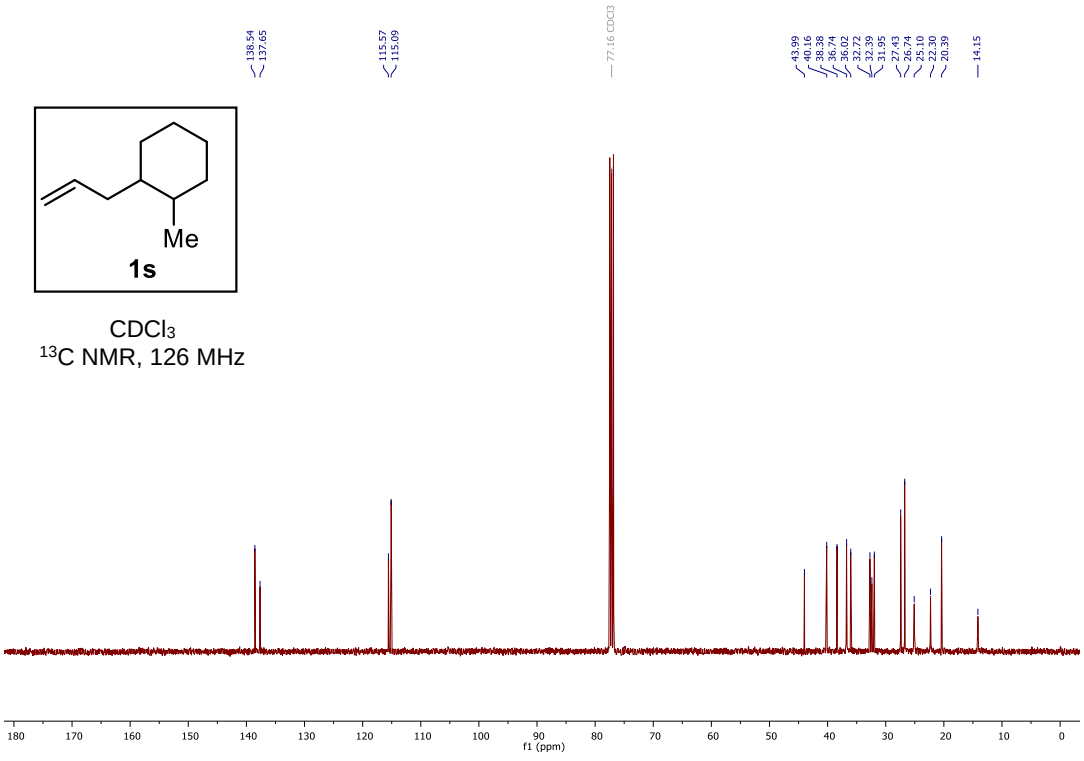
$CDCl_3$
^{13}C NMR, 126 MHz

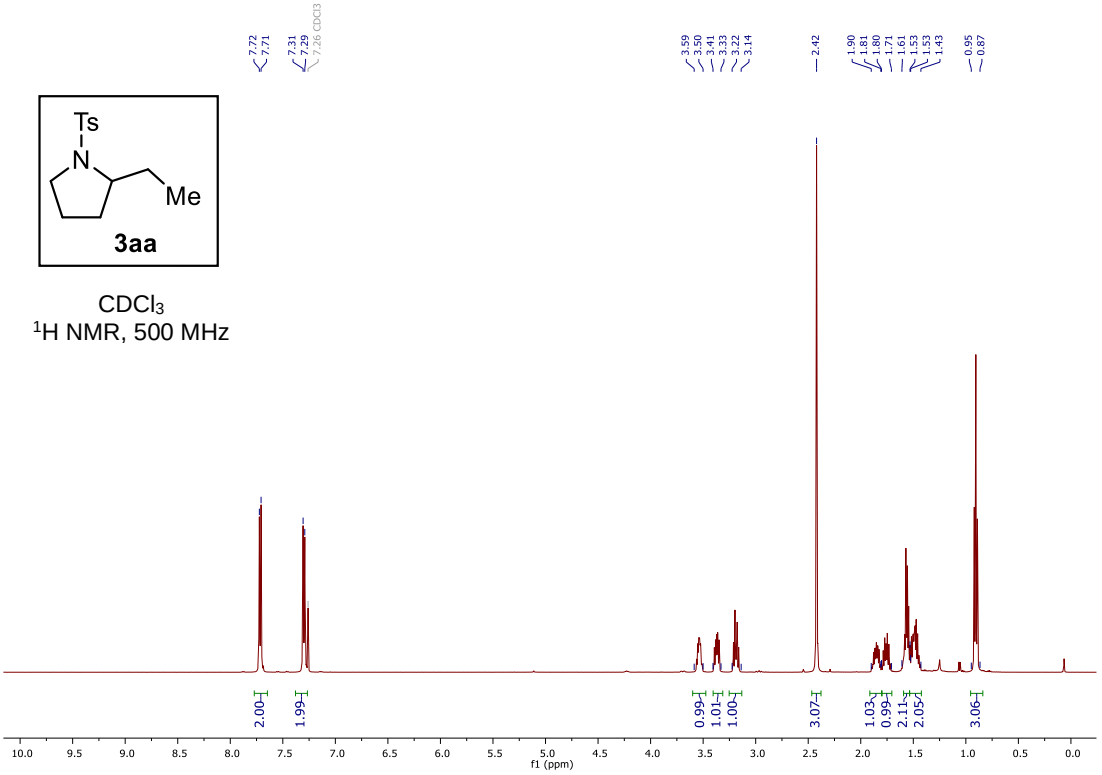


$CDCl_3$
^{1}H NMR, 500 MHz

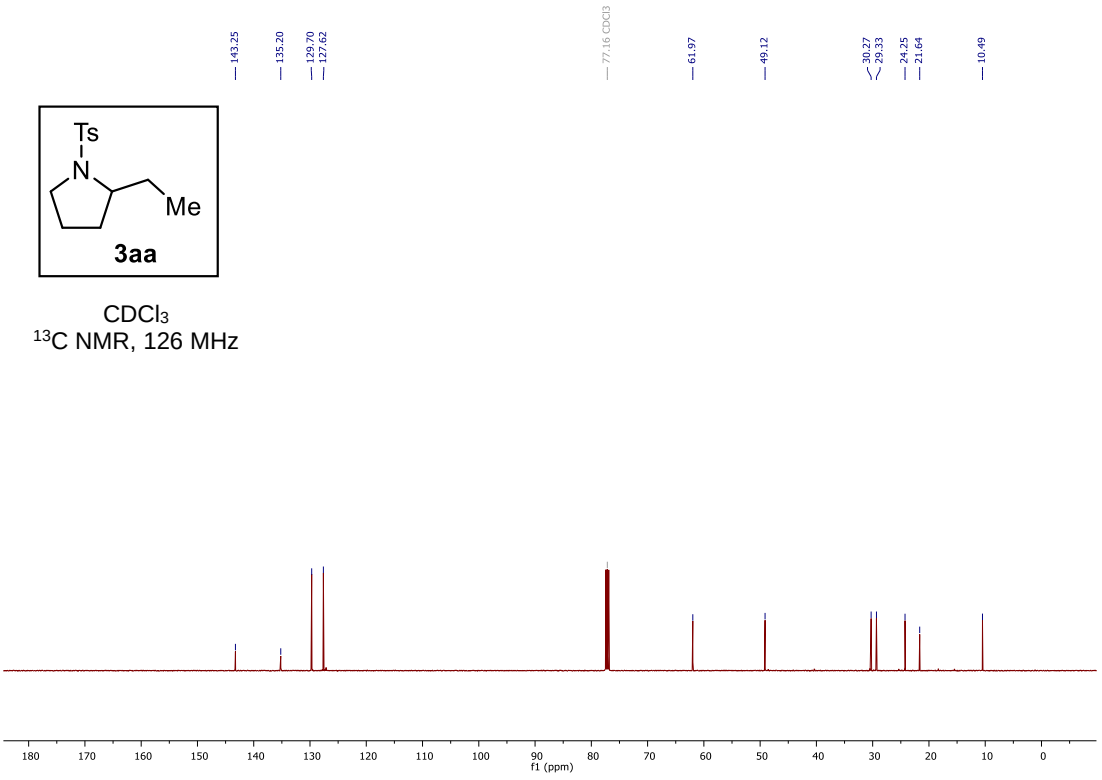


$CDCl_3$
^{13}C NMR, 126 MHz

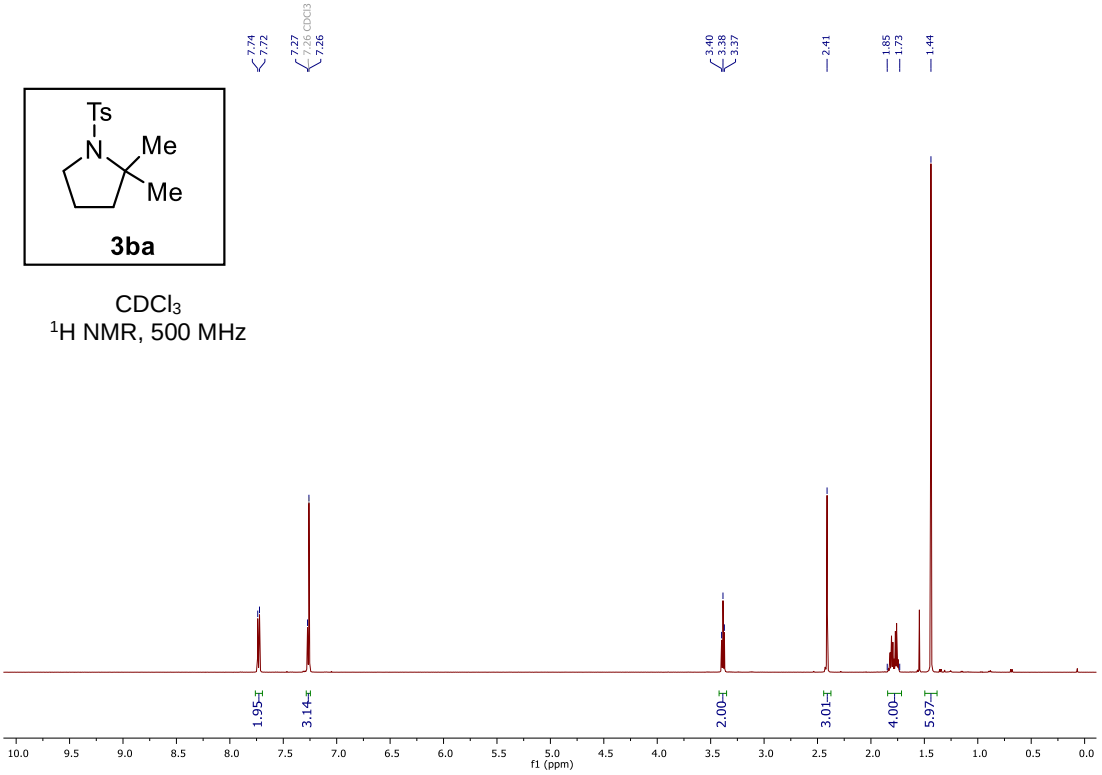




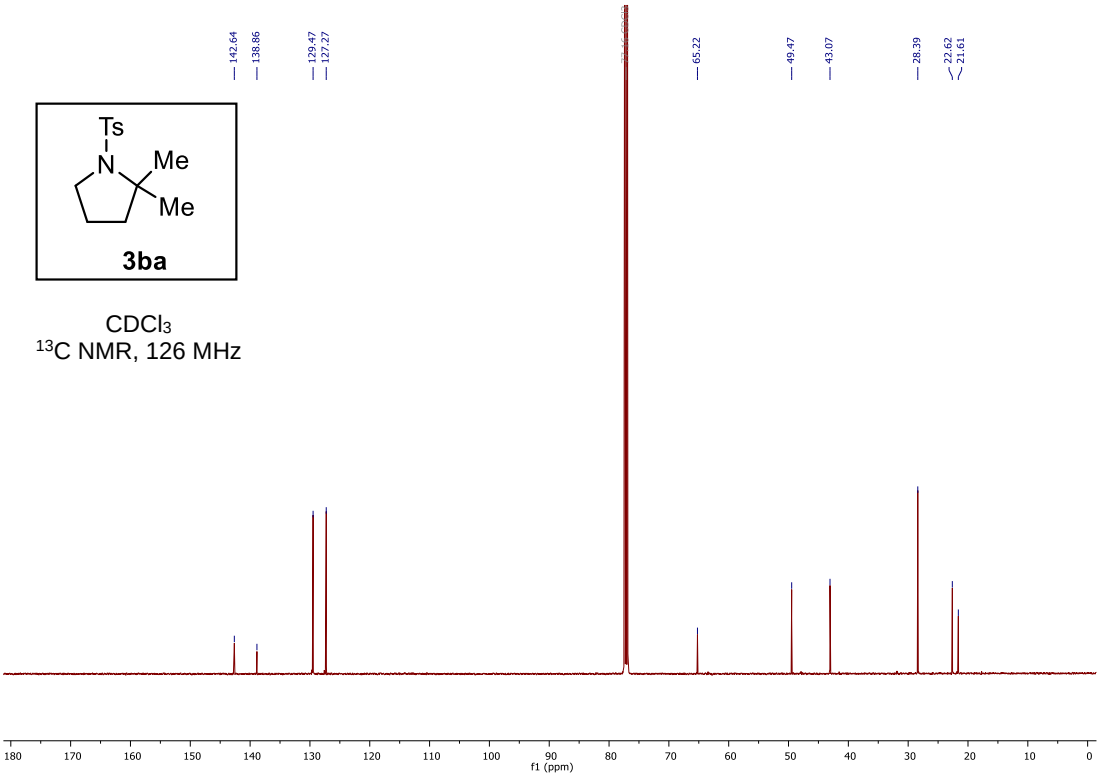
$CDCl_3$
^{1}H NMR, 500 MHz



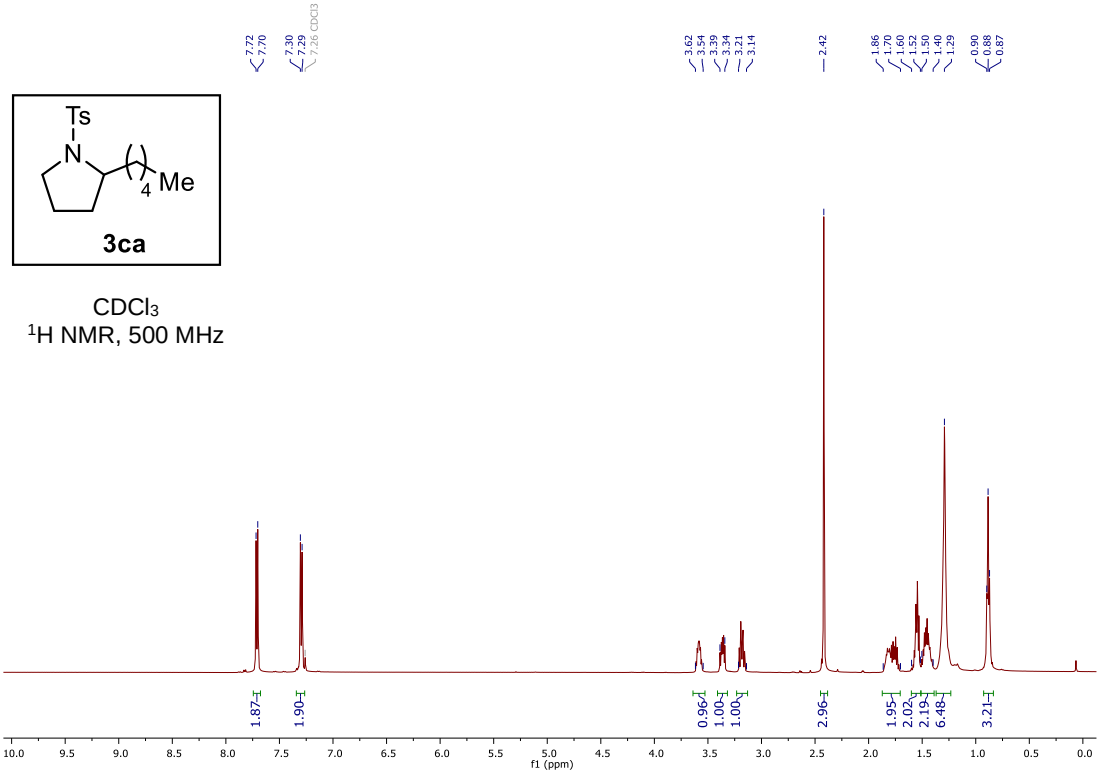
$CDCl_3$
^{13}C NMR, 126 MHz



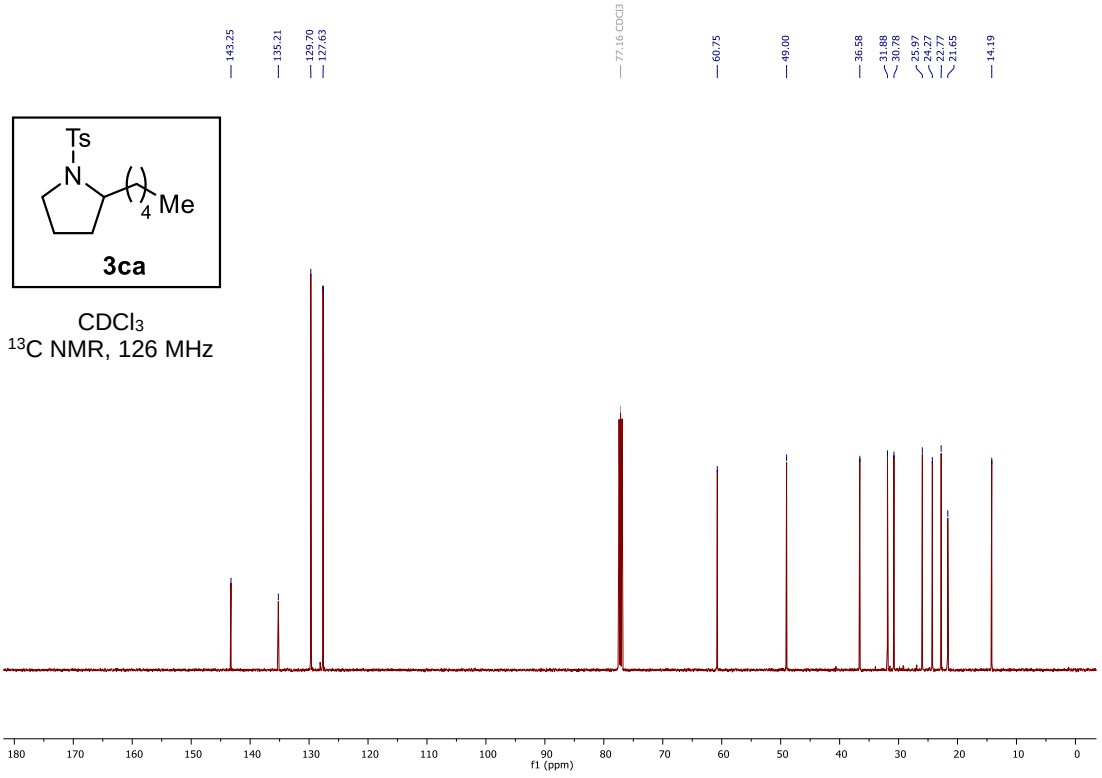
$CDCl_3$
^{1}H NMR, 500 MHz



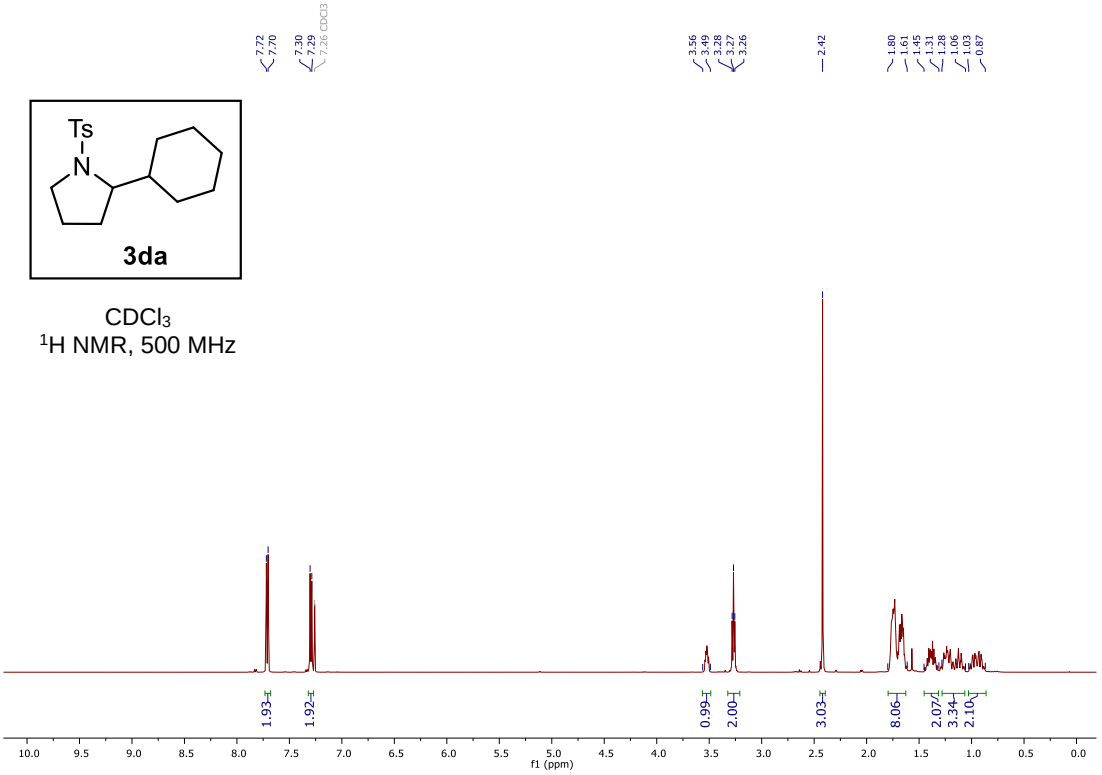
$CDCl_3$
^{13}C NMR, 126 MHz



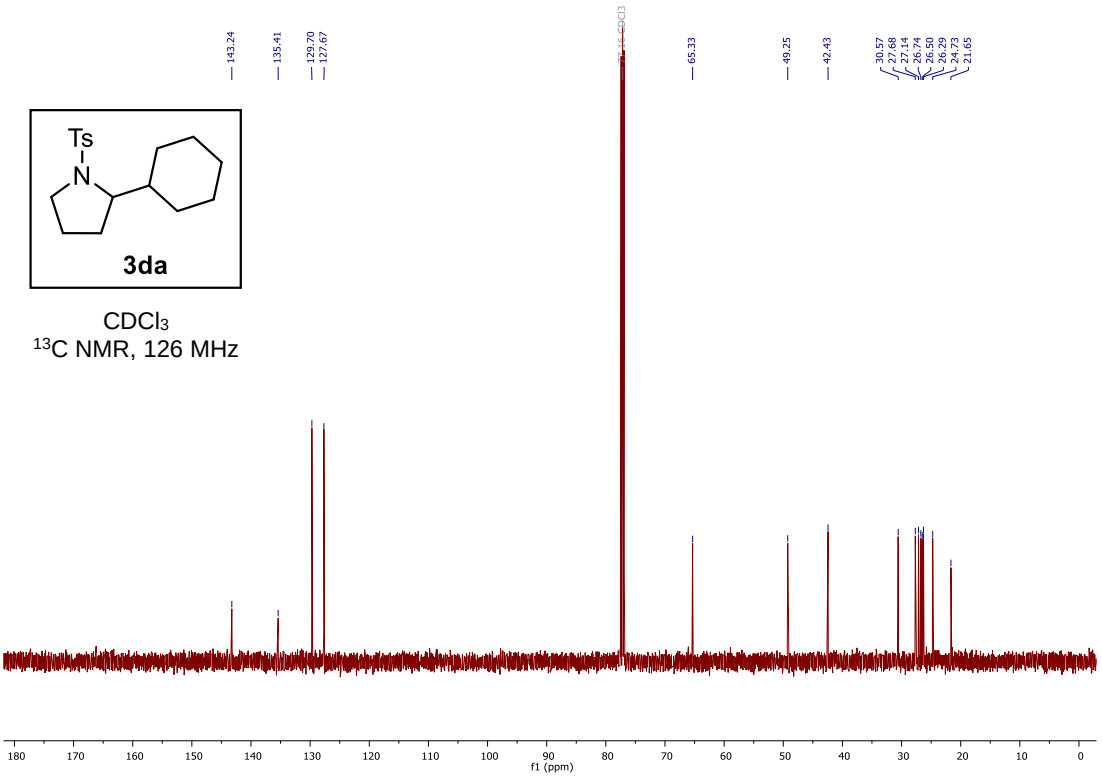
$CDCl_3$
^{1}H NMR, 500 MHz



$CDCl_3$
^{13}C NMR, 126 MHz



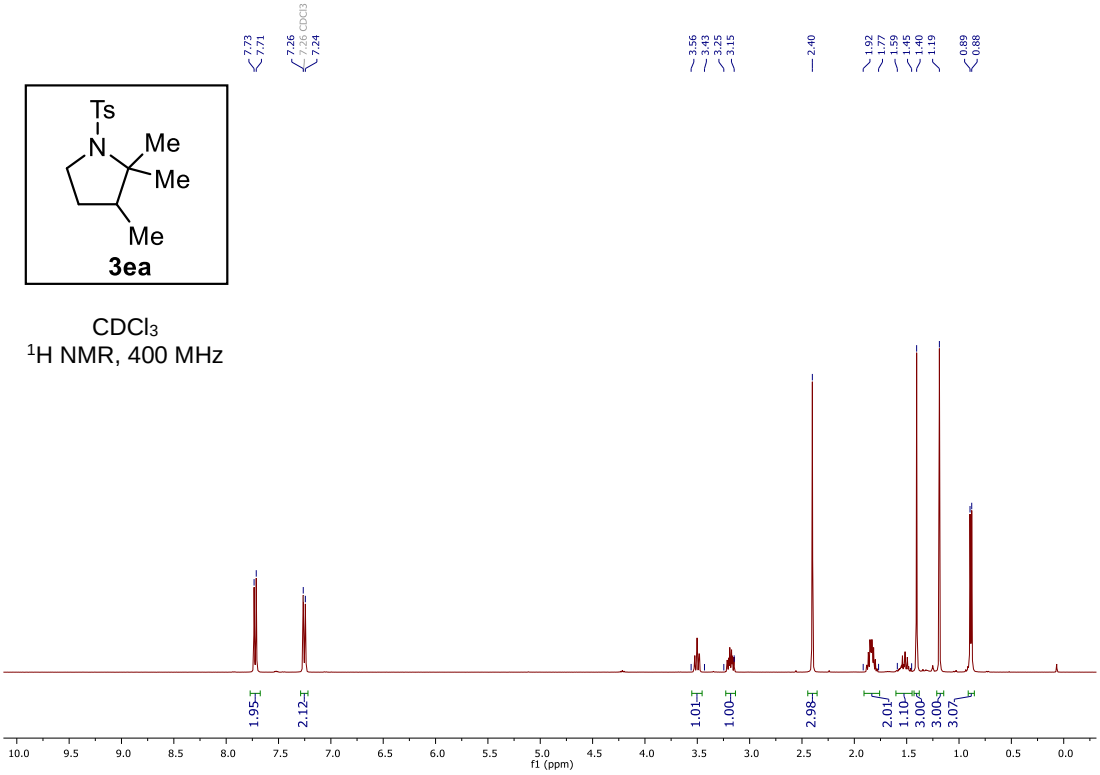
$CDCl_3$
^{1}H NMR, 500 MHz



$CDCl_3$
^{13}C NMR, 126 MHz

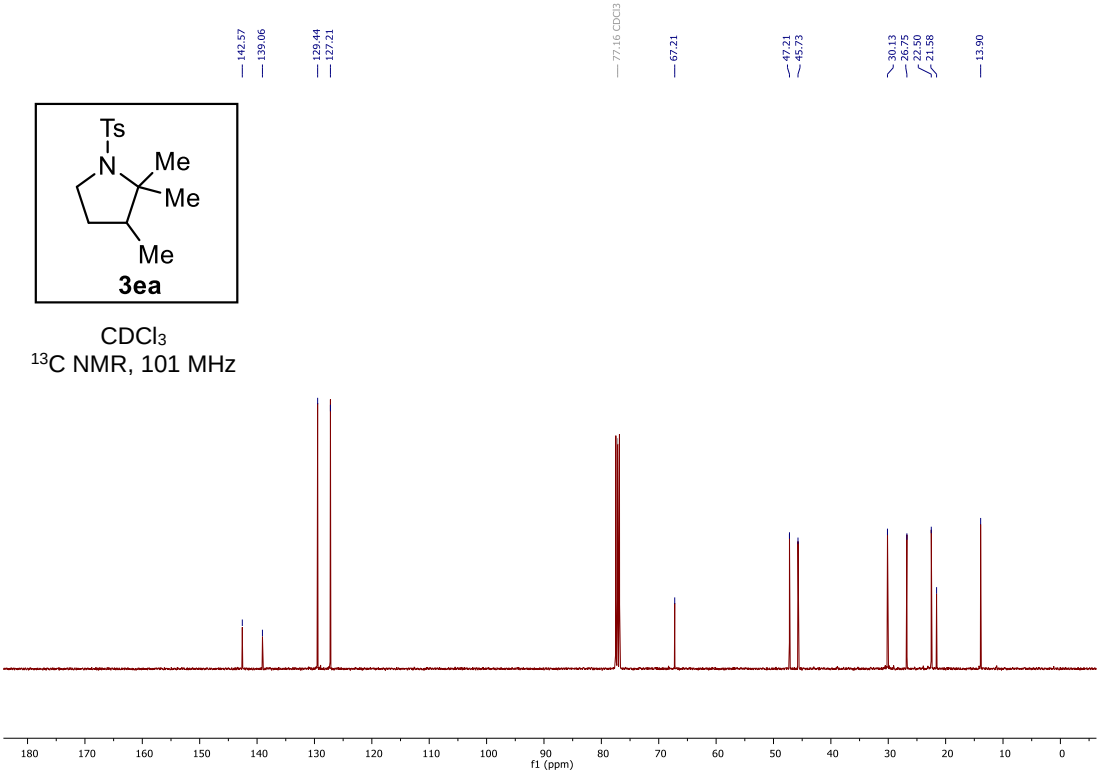
3ea

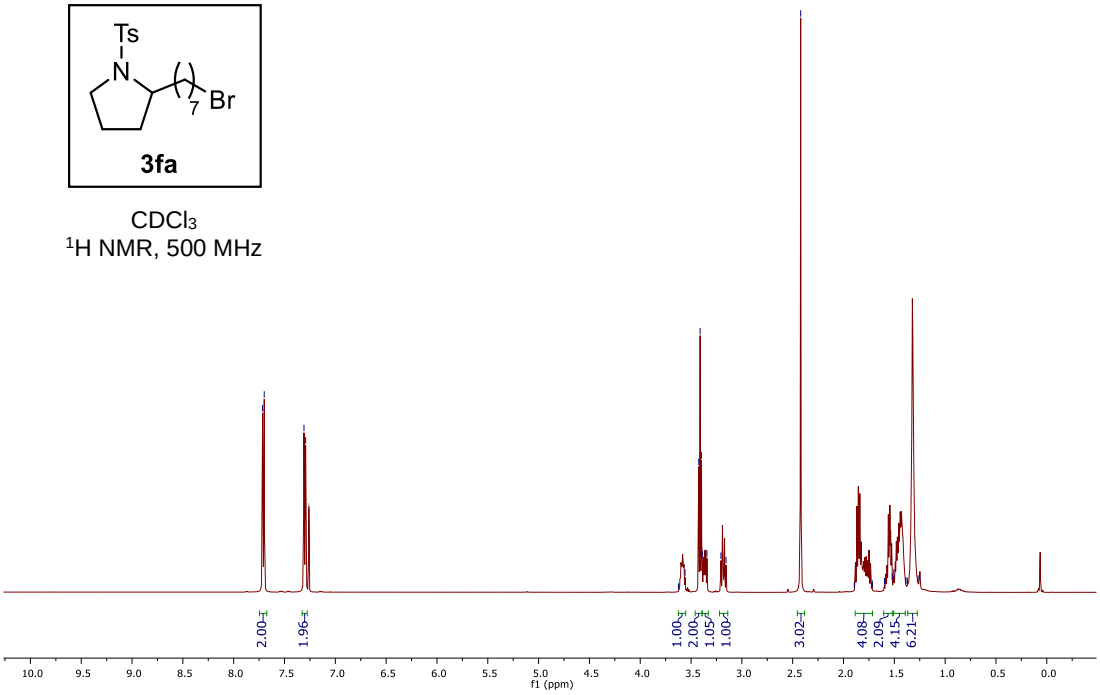
$CDCl_3$
^{1}H NMR, 400 MHz

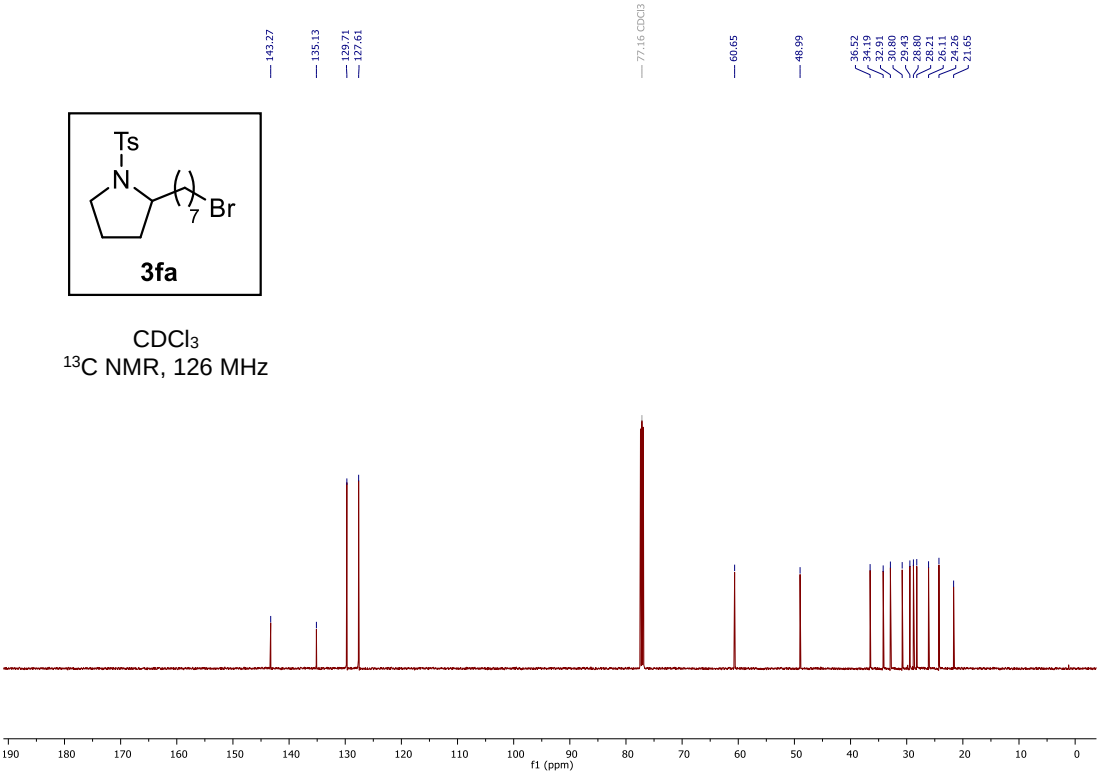


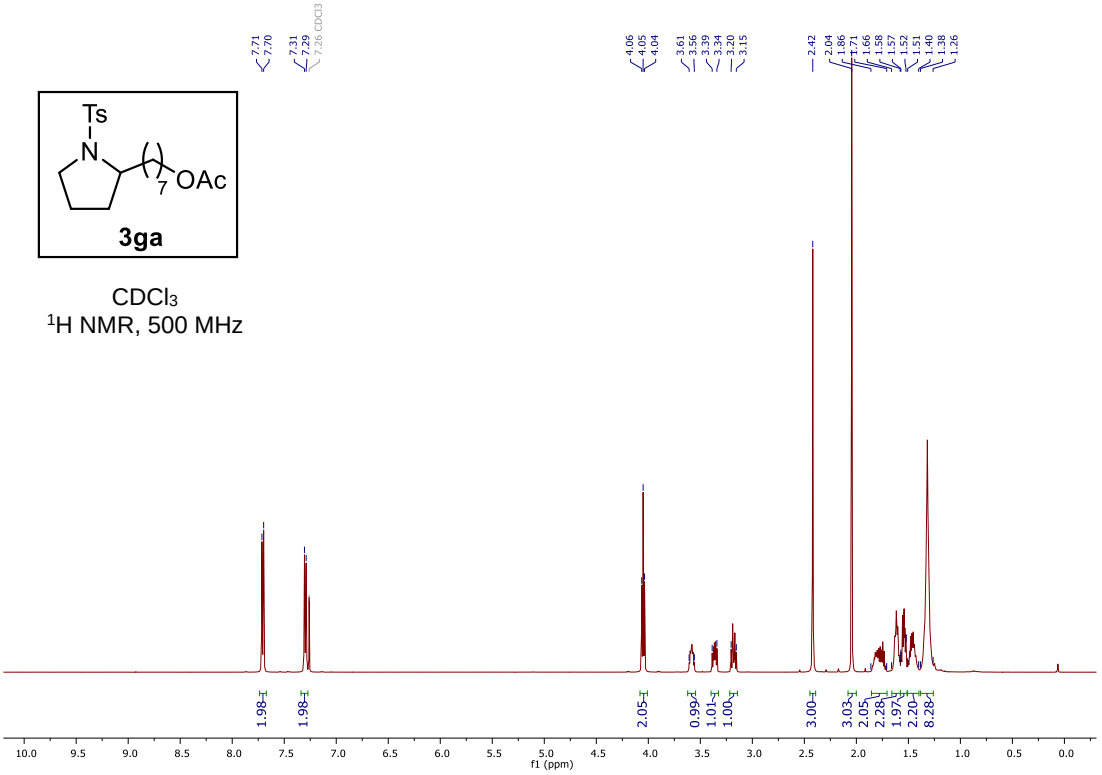
3ea

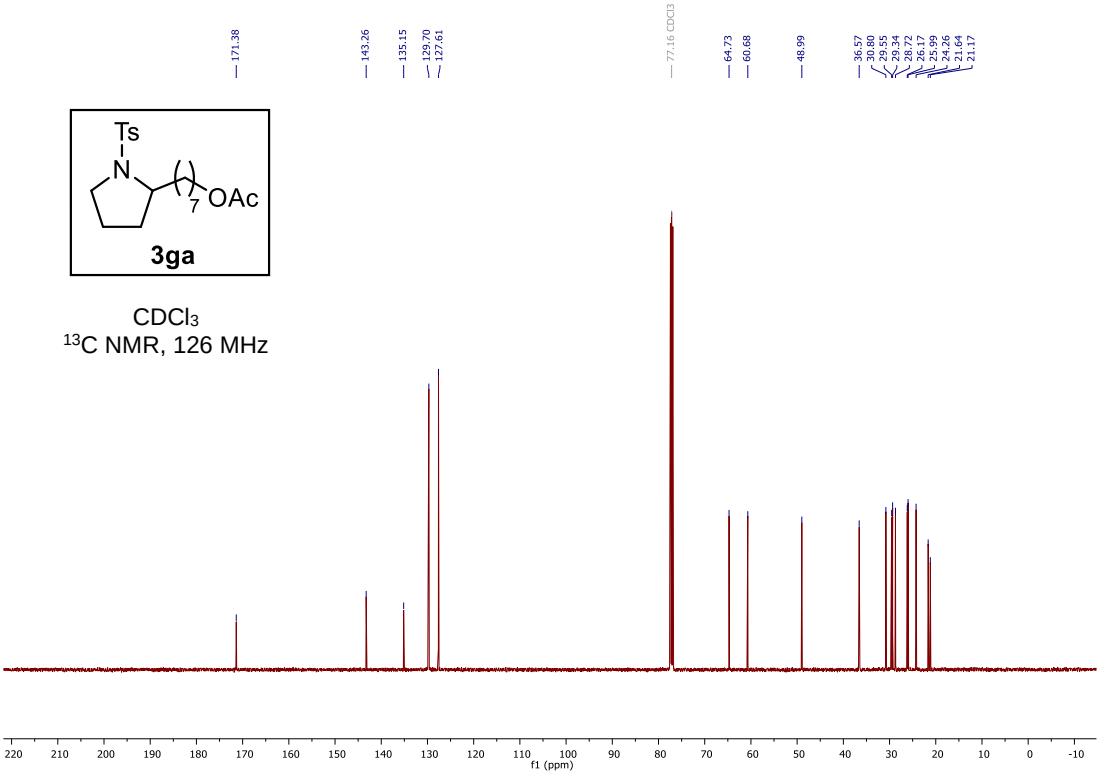
$CDCl_3$
^{13}C NMR, 101 MHz

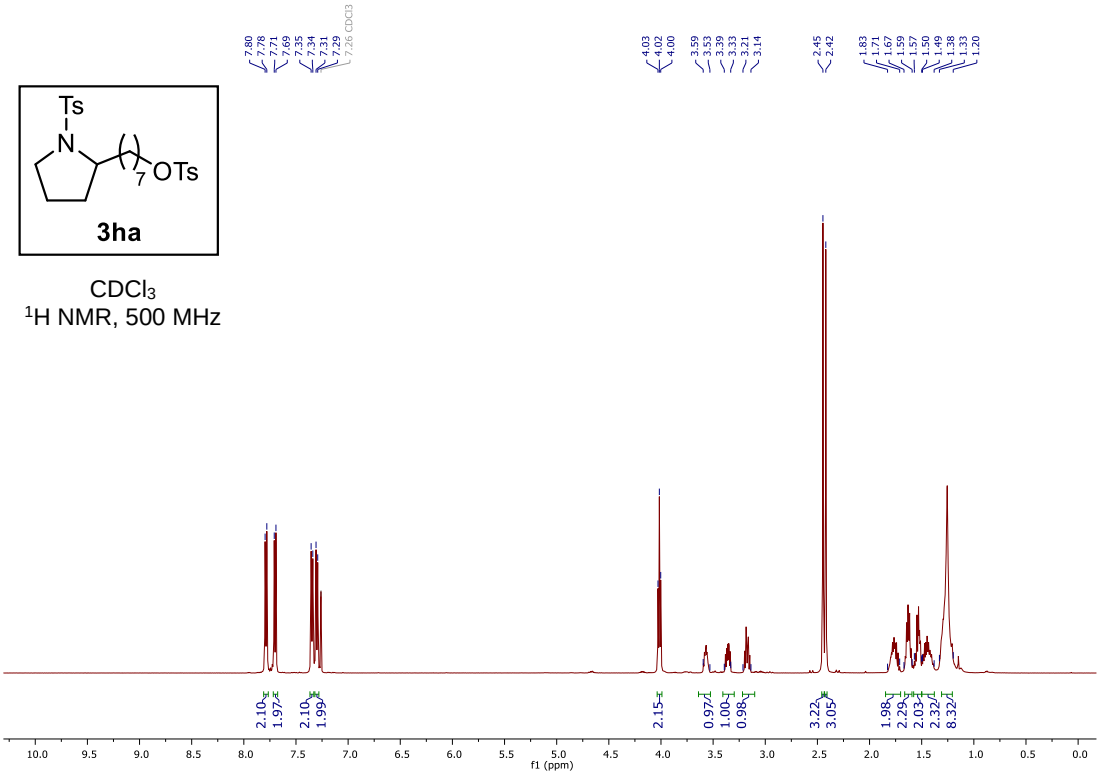


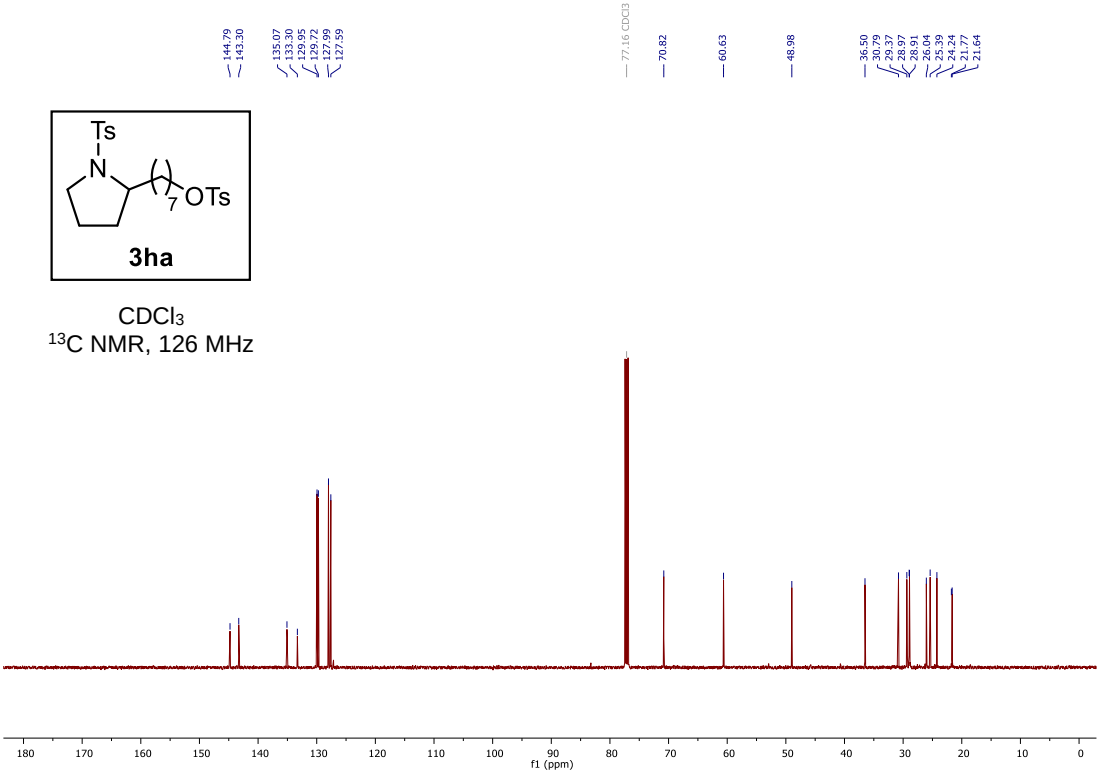

Ts
N
7
Br
3fa
CDCl3
1H NMR, 500 MHz
f1 (ppm)

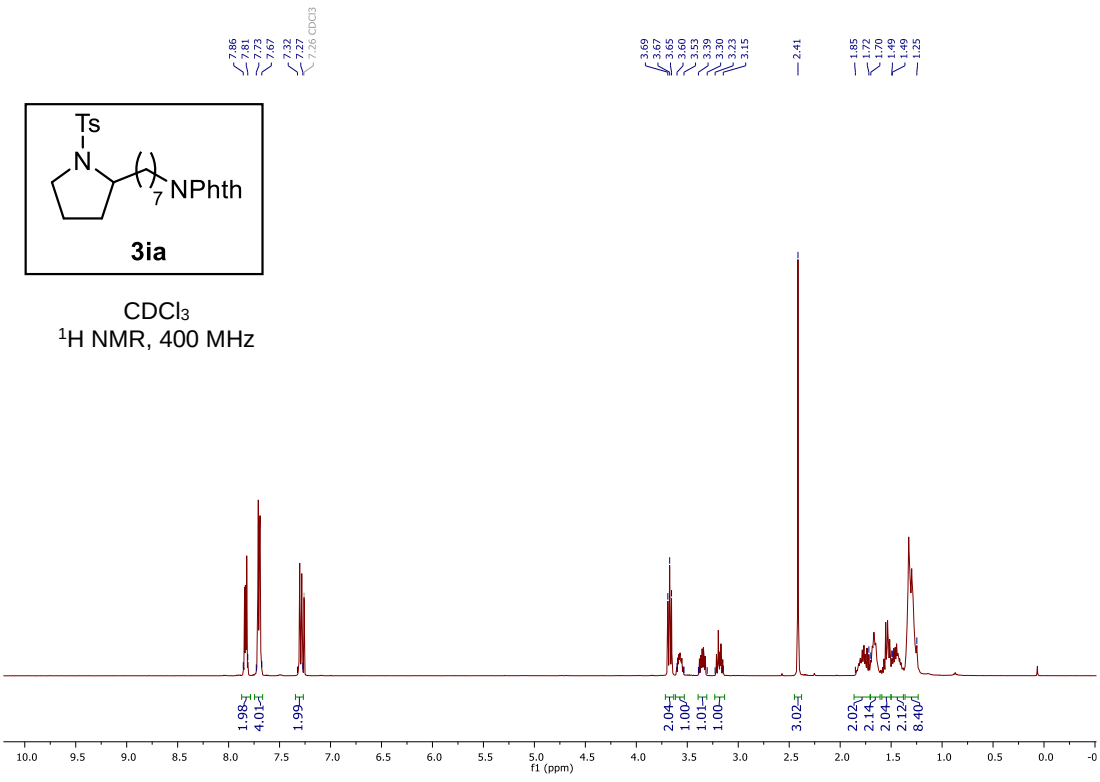

Ts
N
7
Br
3fa
CDCl3
13C NMR, 126 MHz
f1 (ppm)

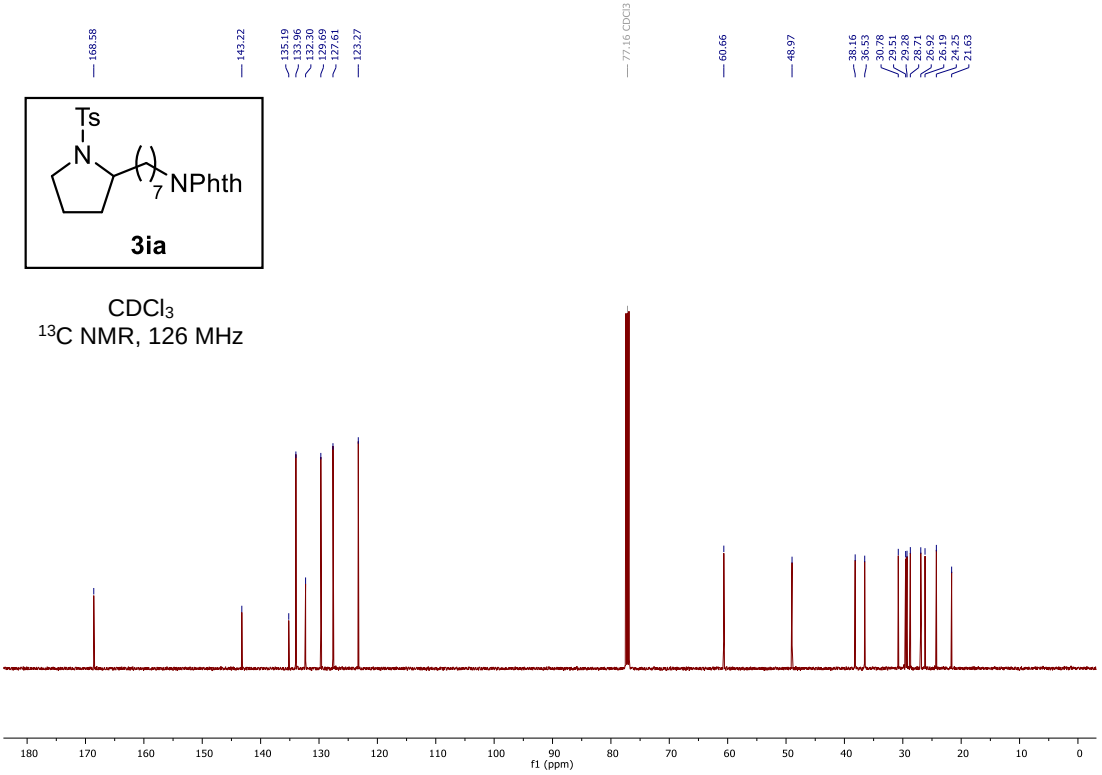

Ts
N
7
OAc
3ga
CDCl3
1H NMR, 500 MHz
f1 (ppm)


Ts
N
7
OAc
3ga
CDCl3
13C NMR, 126 MHz
f1 (ppm)

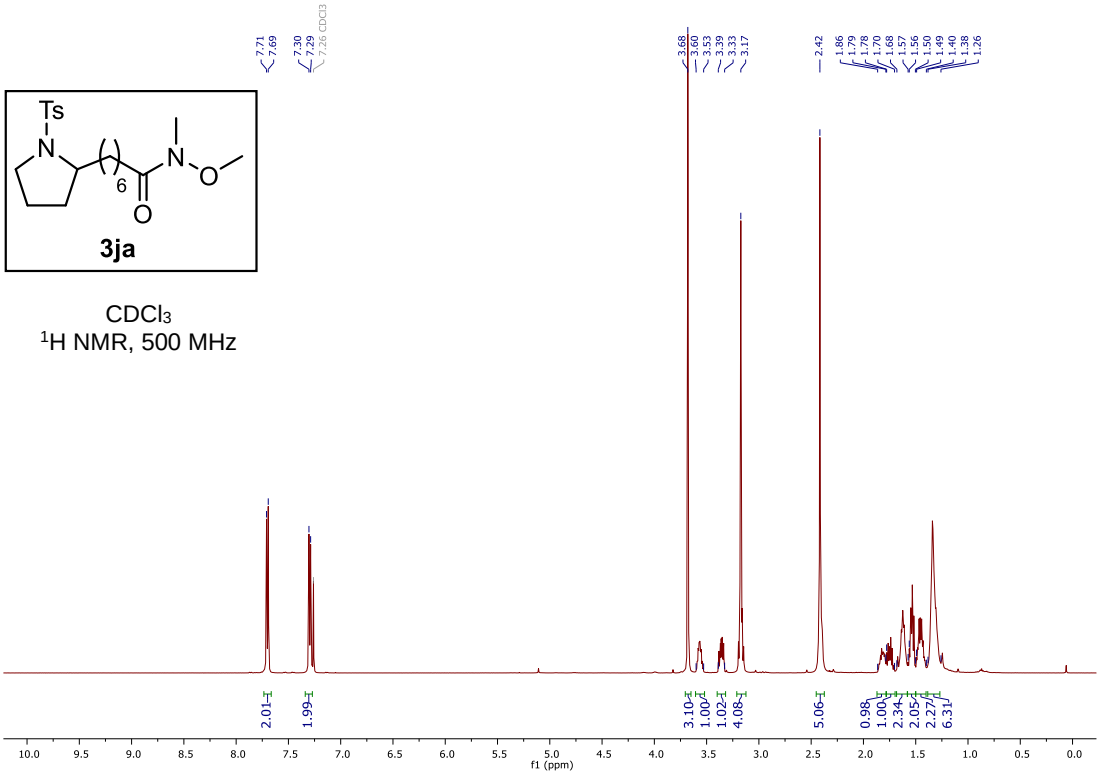

Ts
N
7
OTs
3ha
CDCl3
1H NMR, 500 MHz
f1 (ppm)


144.79
143.30
135.07
133.30
129.95
129.72
127.99
127.59
77.16 CDCl3
70.82
60.63
48.98
36.50
30.79
29.37
28.97
28.91
26.04
25.39
24.24
21.77
21.64
Ts
N
7
OTs
3ha
CDCl3
13C NMR, 126 MHz
f1 (ppm)


7.86
7.81
7.73
7.67
7.32
7.27
7.26 CDCl3
3.69
3.67
3.65
3.60
3.53
3.39
3.30
3.23
3.15
2.41
1.85
1.72
1.70
1.49
1.49
1.25
Ts
N
7
NPhth
3ia
CDCl3
1H NMR, 400 MHz
1.98
4.01
1.99
2.04
1.00
1.01
1.00
3.02
2.02
2.14
2.04
2.12
8.40
f1 (ppm)



$CDCl_3$
^{13}C NMR, 126 MHz

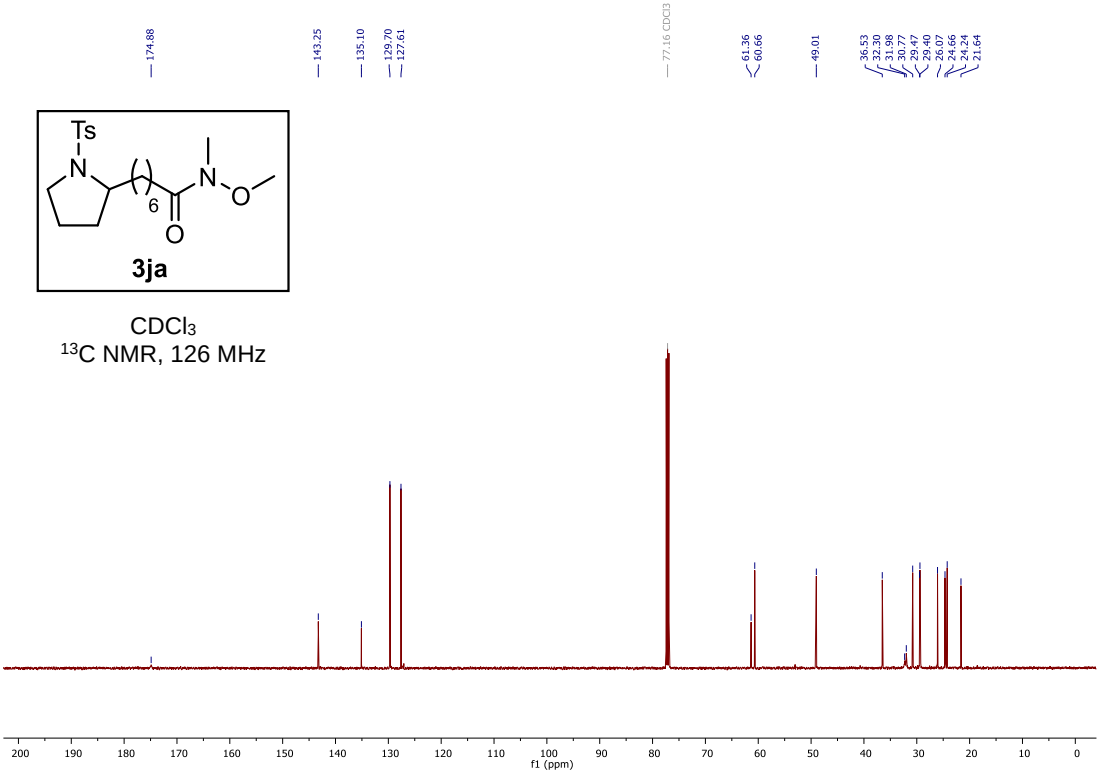


$CDCl_3$
^{1}H NMR, 500 MHz

3ja

$CDCl_3$

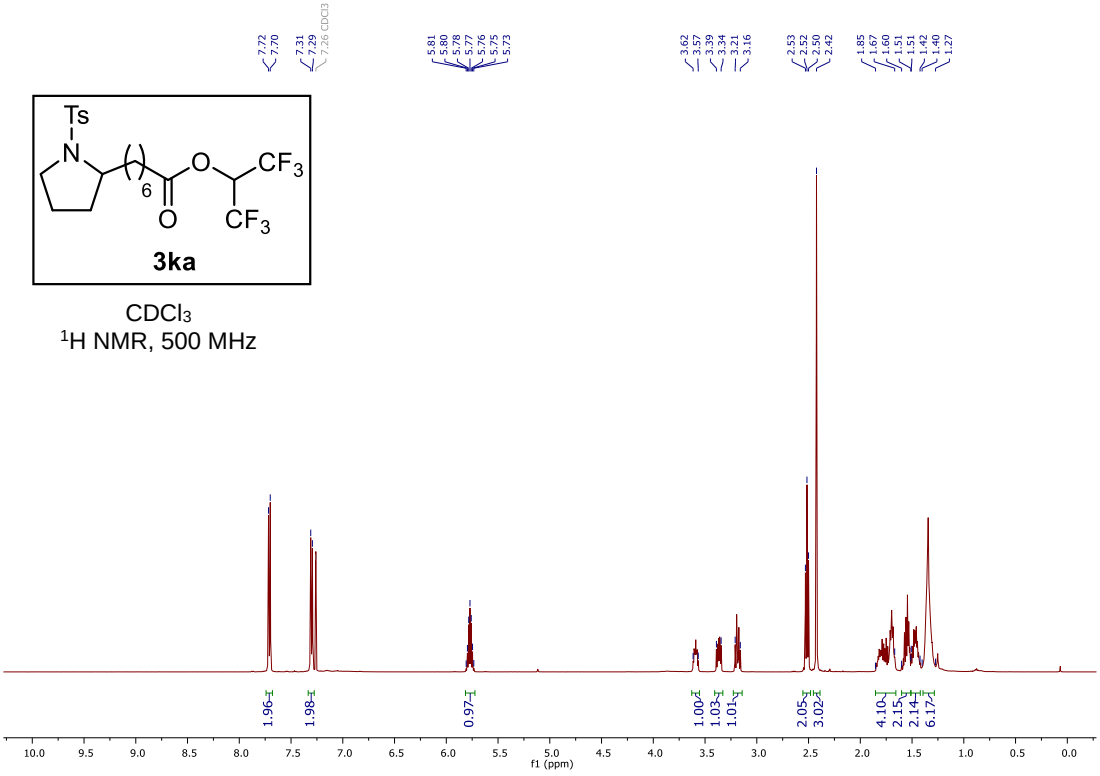
^{13}C NMR, 126 MHz

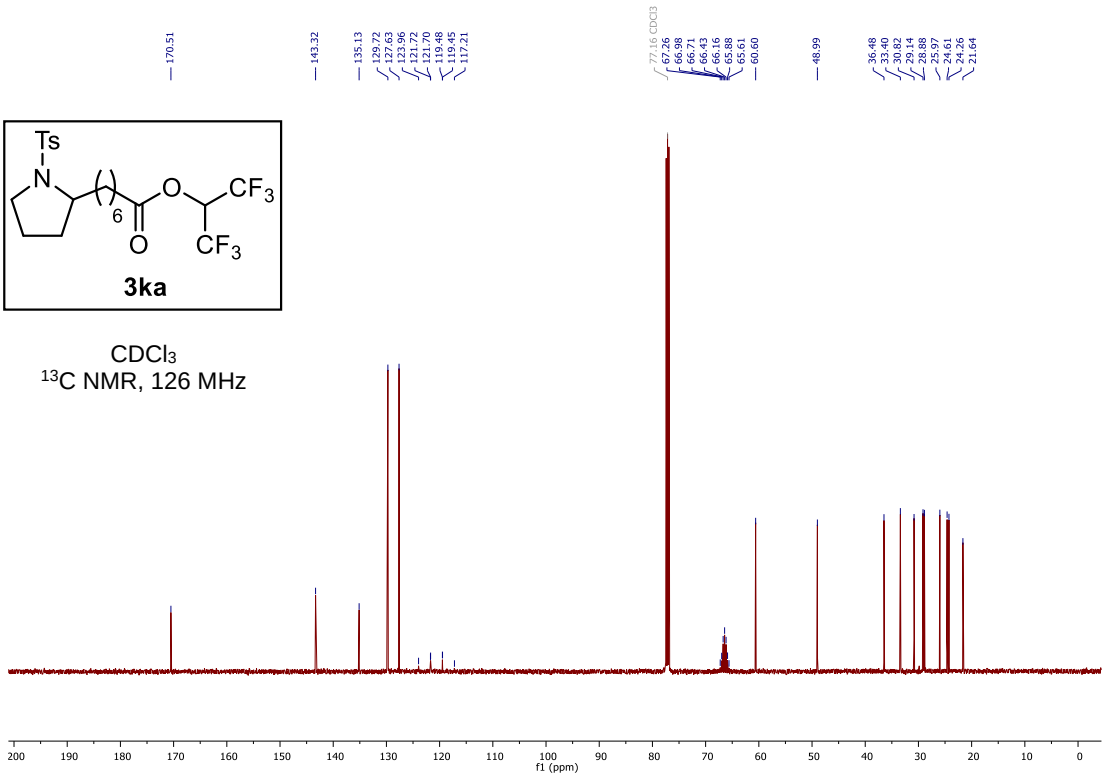


3ka

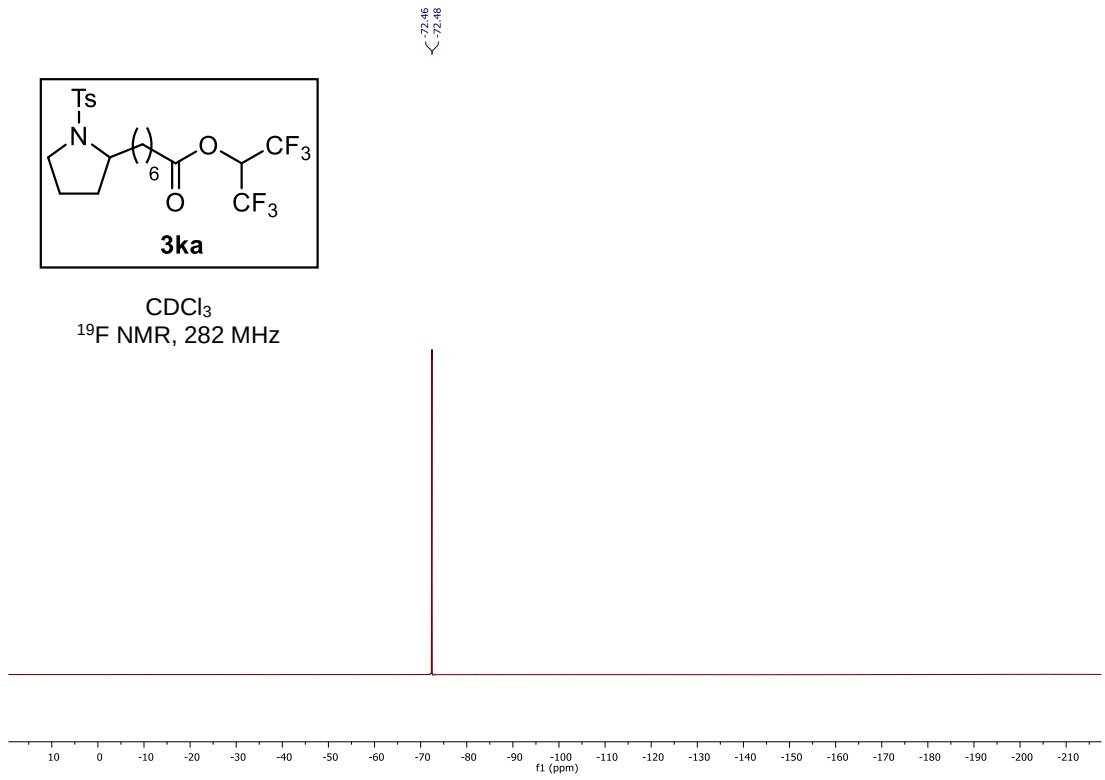
$CDCl_3$

^{1}H NMR, 500 MHz

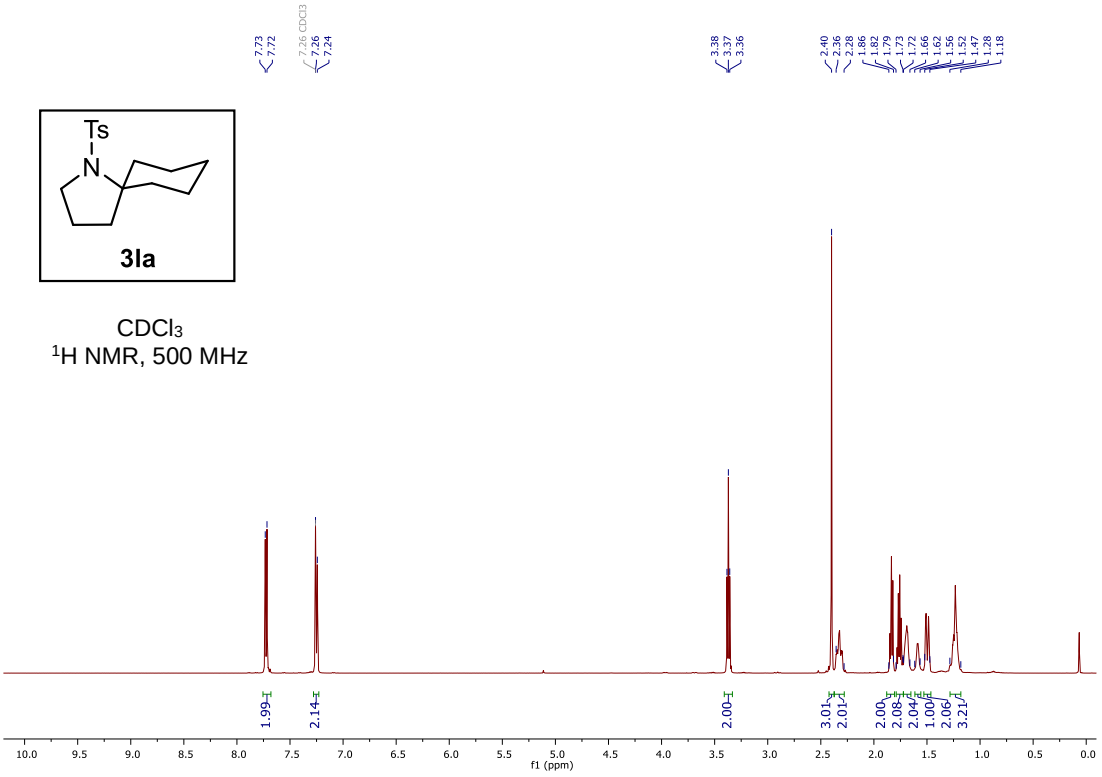




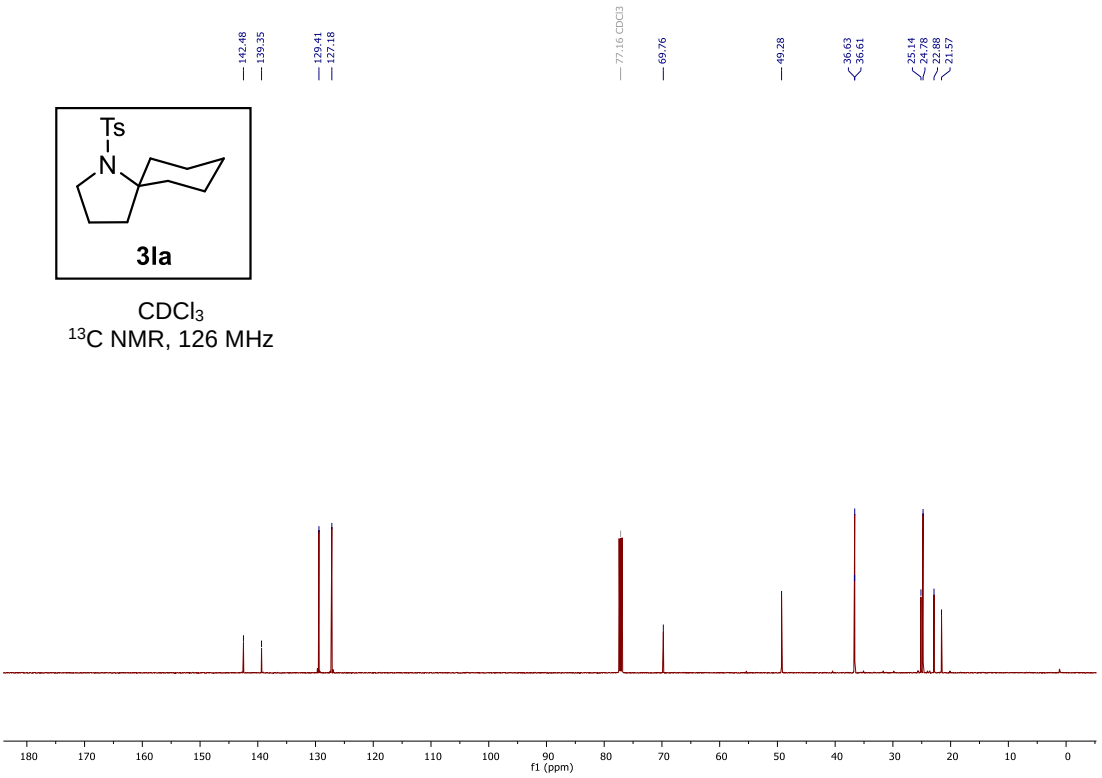
$CDCl_3$
^{13}C NMR, 126 MHz



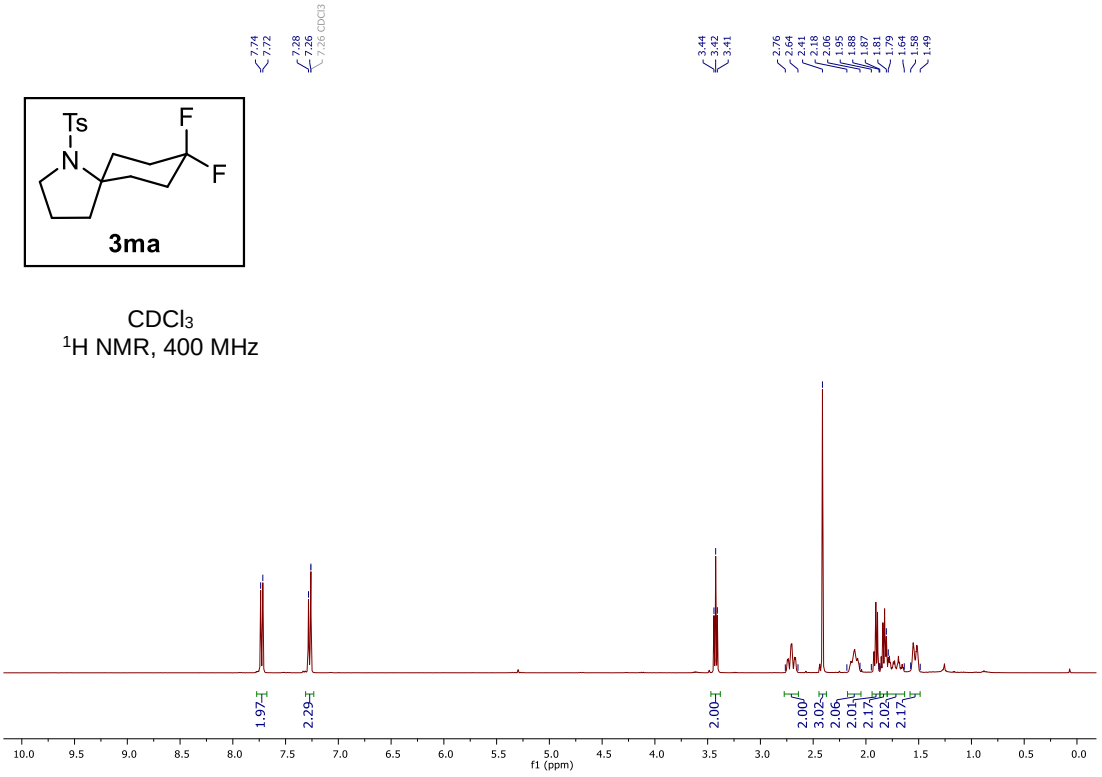
$CDCl_3$
^{19}F NMR, 282 MHz

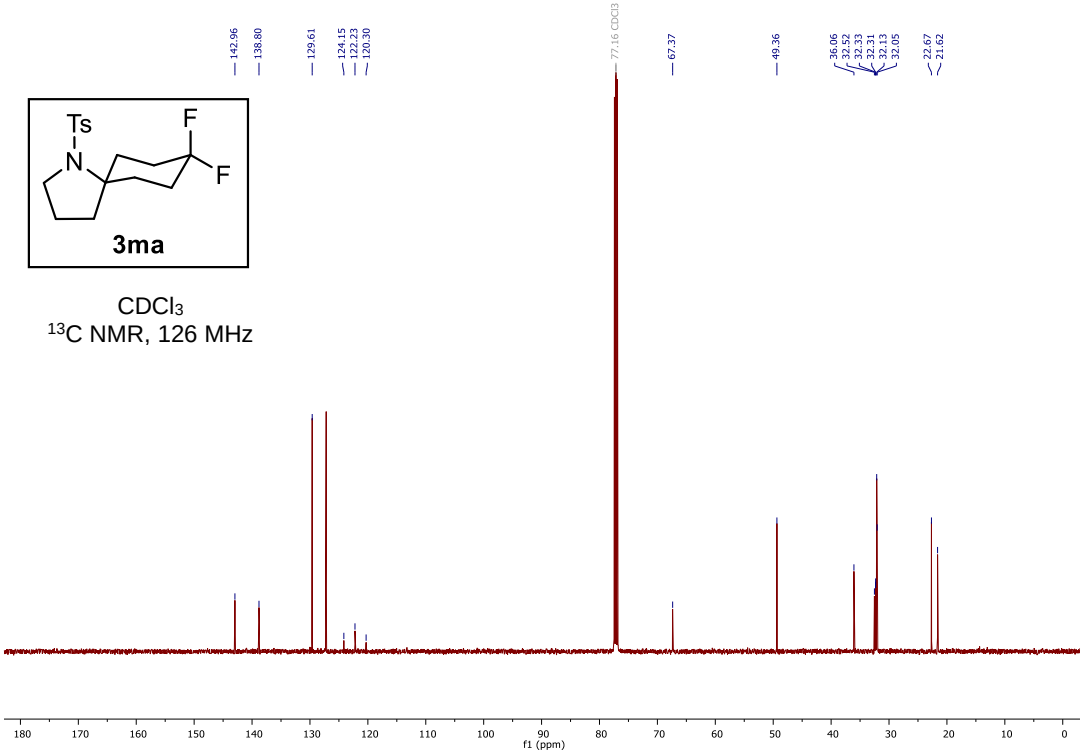

Ts
N
3Ia
CDCl3
1H NMR, 500 MHz
7.73
7.72
7.26 CDCl3
7.26
7.24
3.38
3.37
3.36
2.40
2.36
2.28
1.86
1.82
1.79
1.73
1.72
1.66
1.62
1.56
1.52
1.47
1.28
1.18
1.99
2.14
2.00
3.01
2.01
2.00
2.08
2.04
1.00
2.06
3.21
f1 (ppm)

$CDCl_3$
^{13}C NMR, 126 MHz

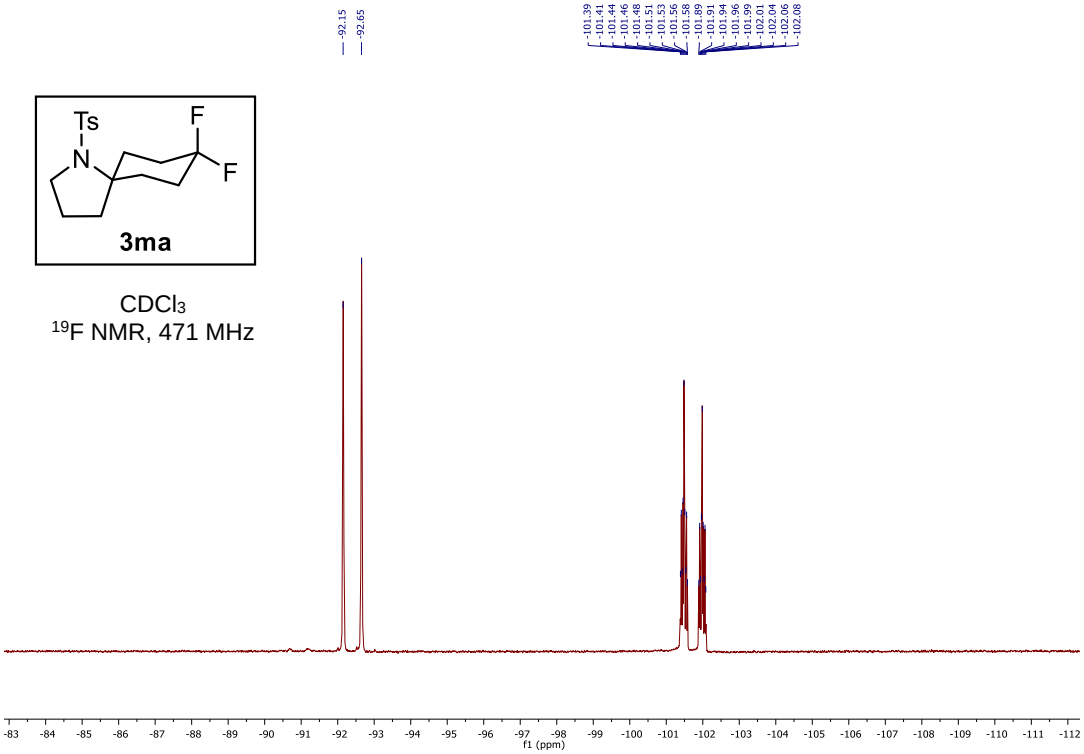


$CDCl_3$
^{1}H NMR, 400 MHz

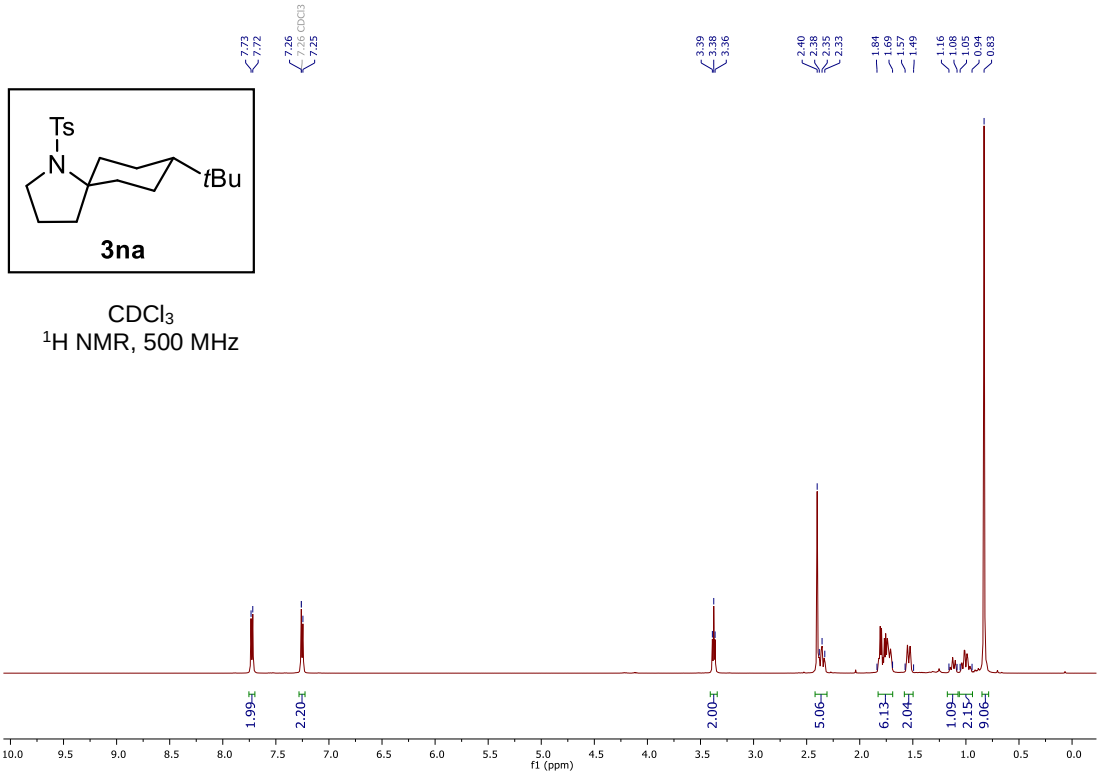




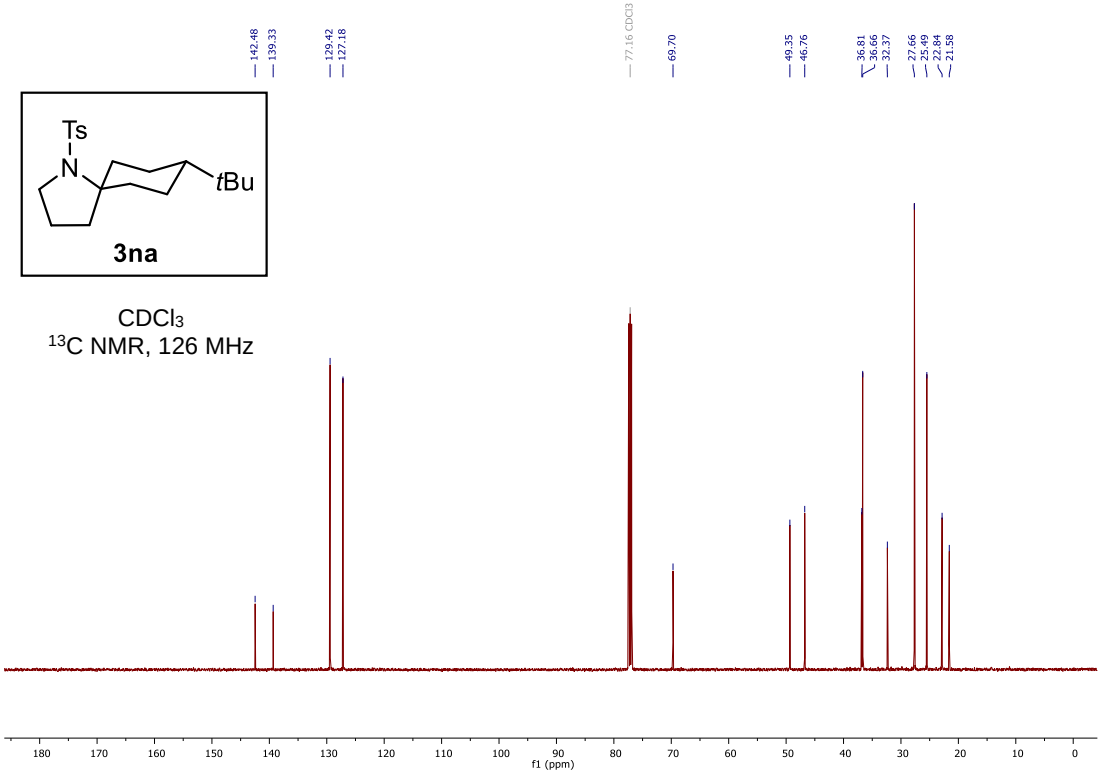
$CDCl_3$
^{13}C NMR, 126 MHz



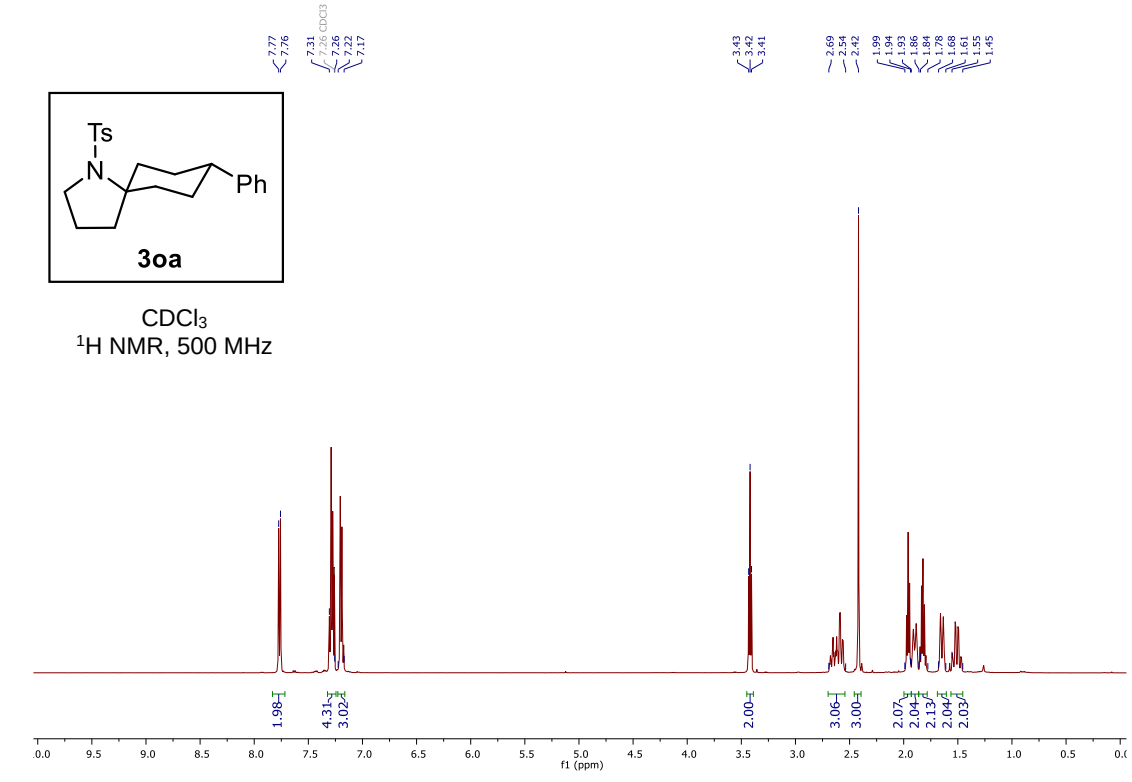
$CDCl_3$
^{19}F NMR, 471 MHz



$CDCl_3$
^{1}H NMR, 500 MHz

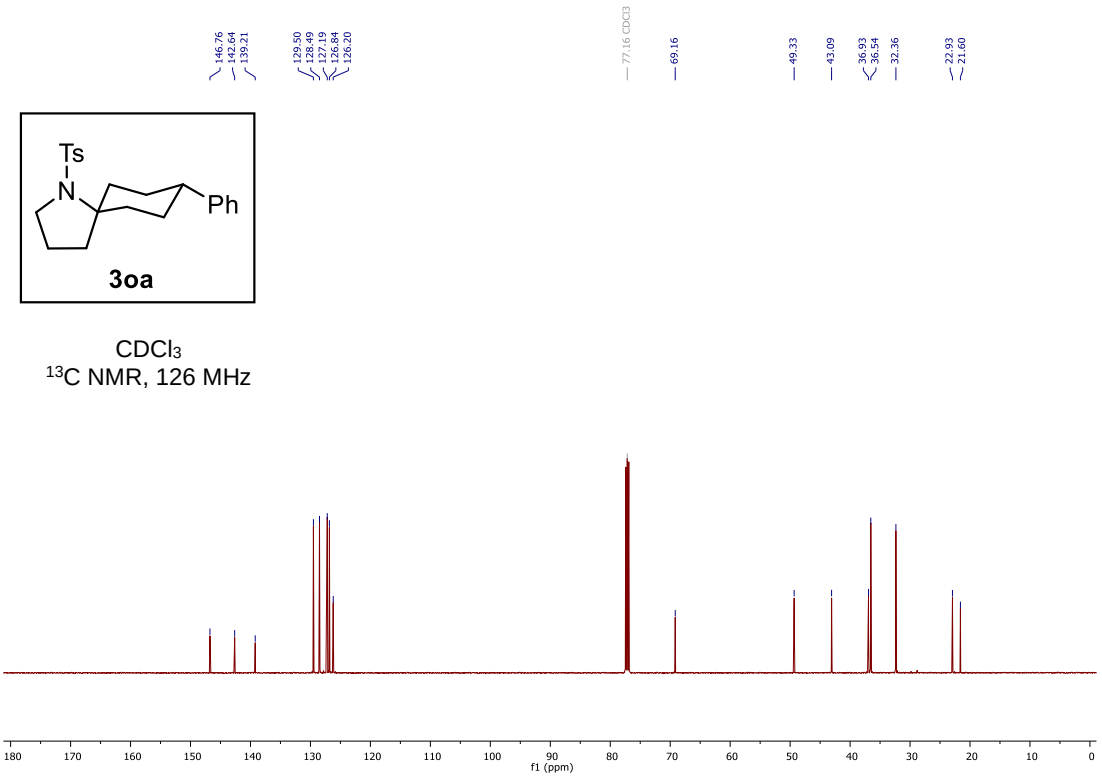


$CDCl_3$
^{13}C NMR, 126 MHz

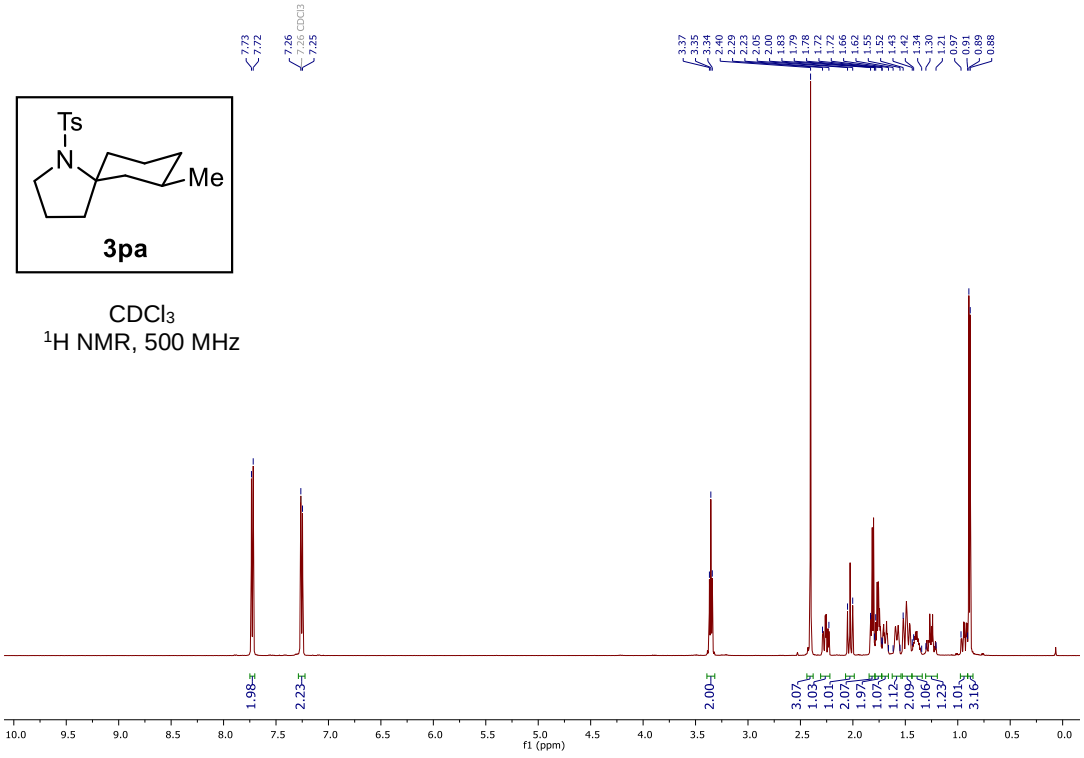


$CDCl_3$
^{1}H NMR, 500 MHz

$CDCl_3$
^{13}C NMR, 126 MHz

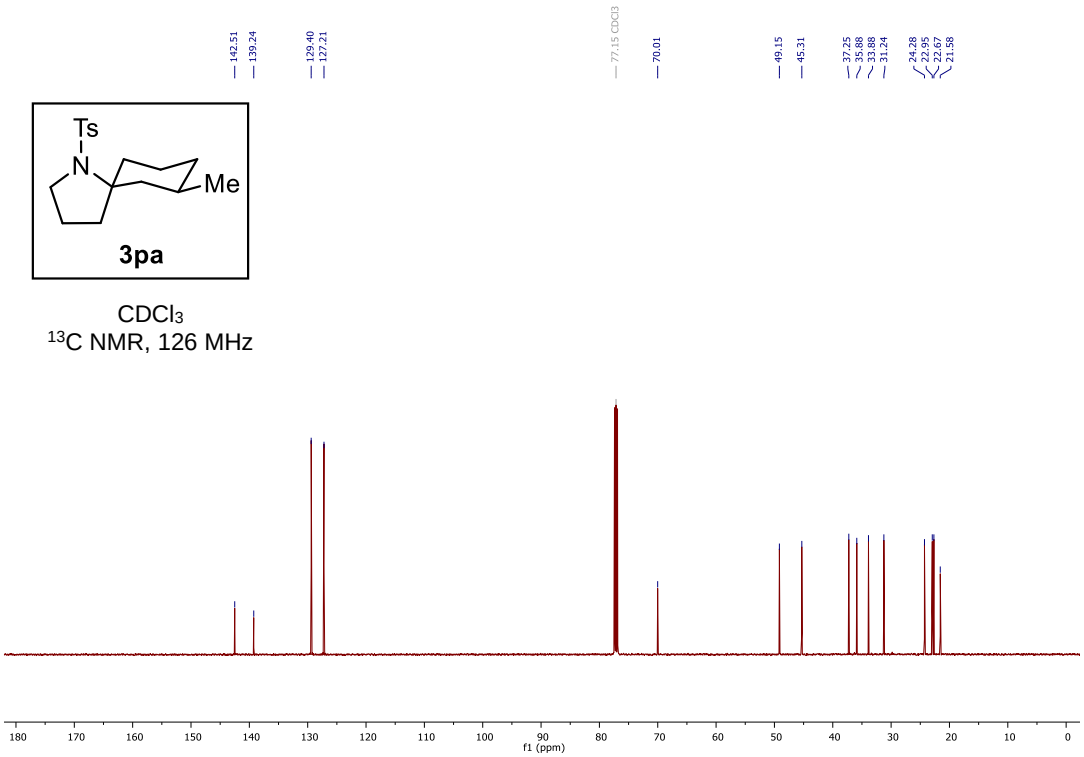


$CDCl_3$
^{1}H NMR, 500 MHz



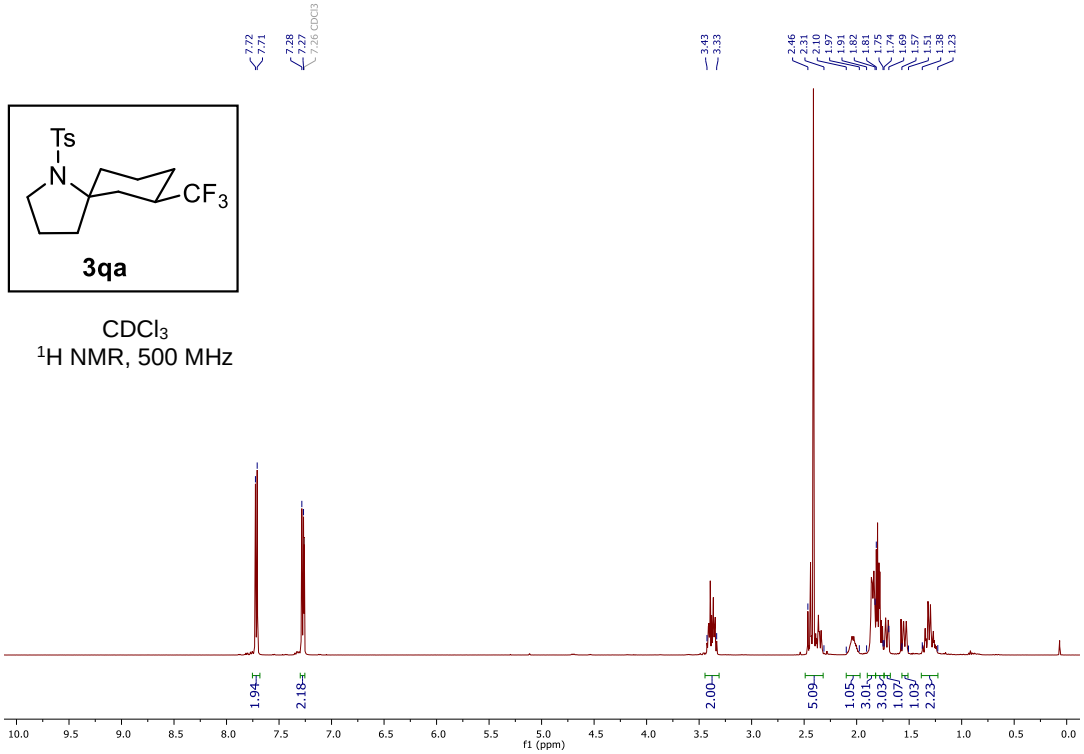
3pa

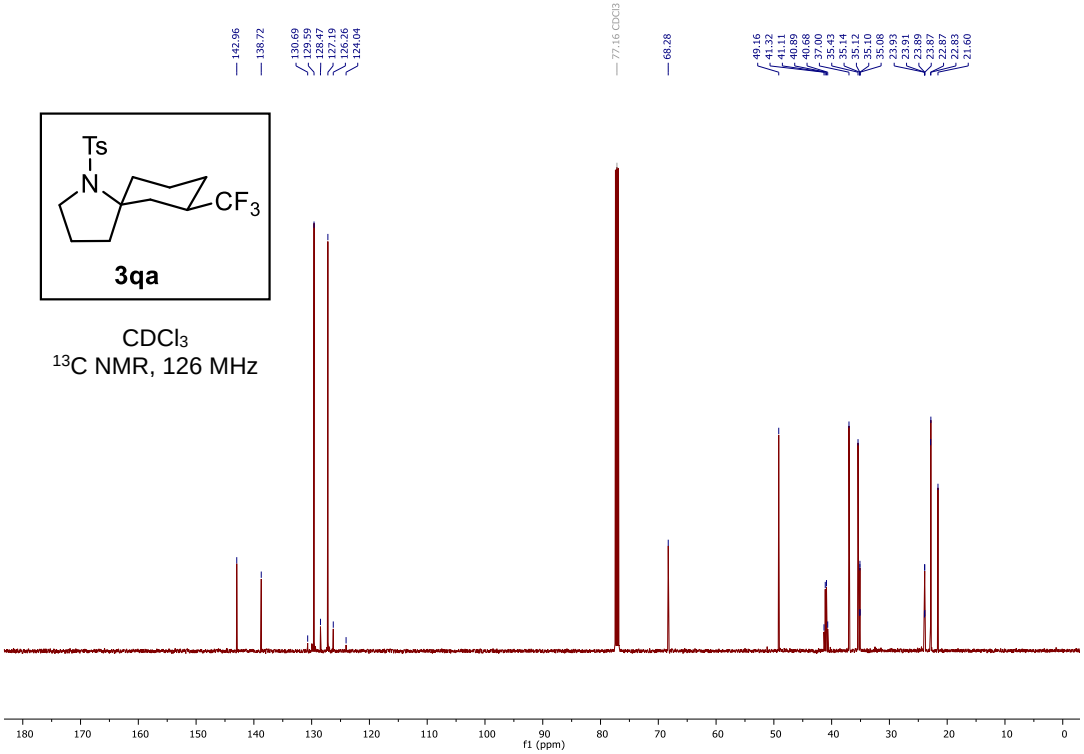
$CDCl_3$
^{13}C NMR, 126 MHz



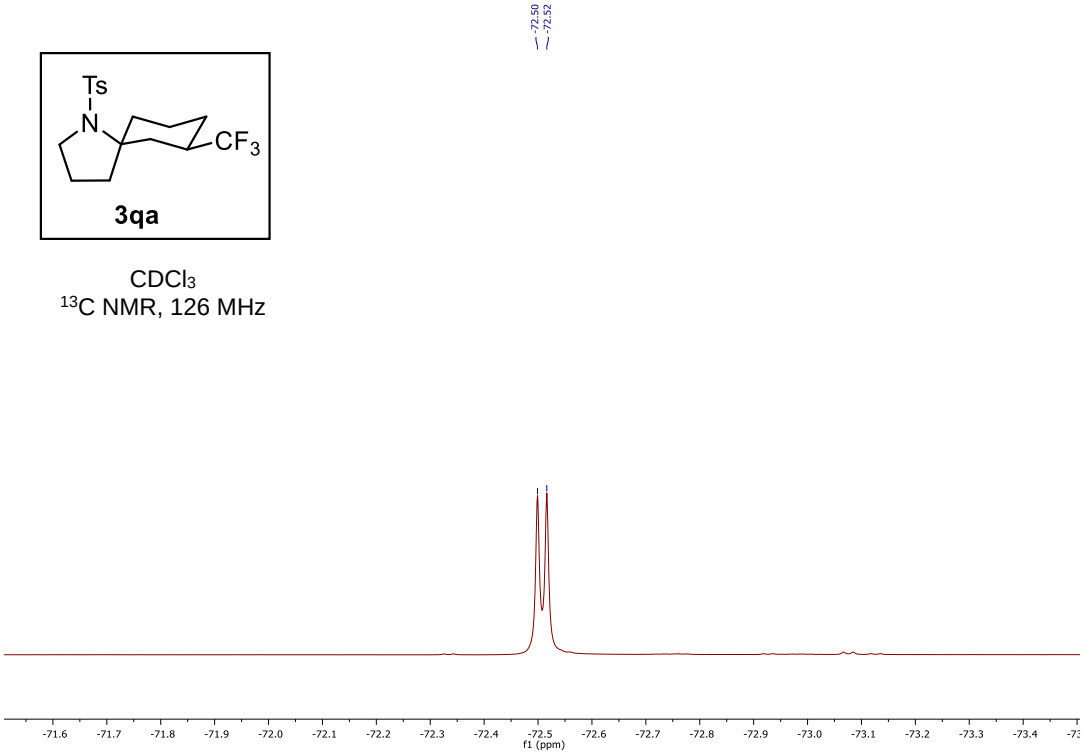
3qa

$CDCl_3$
^{1}H NMR, 500 MHz





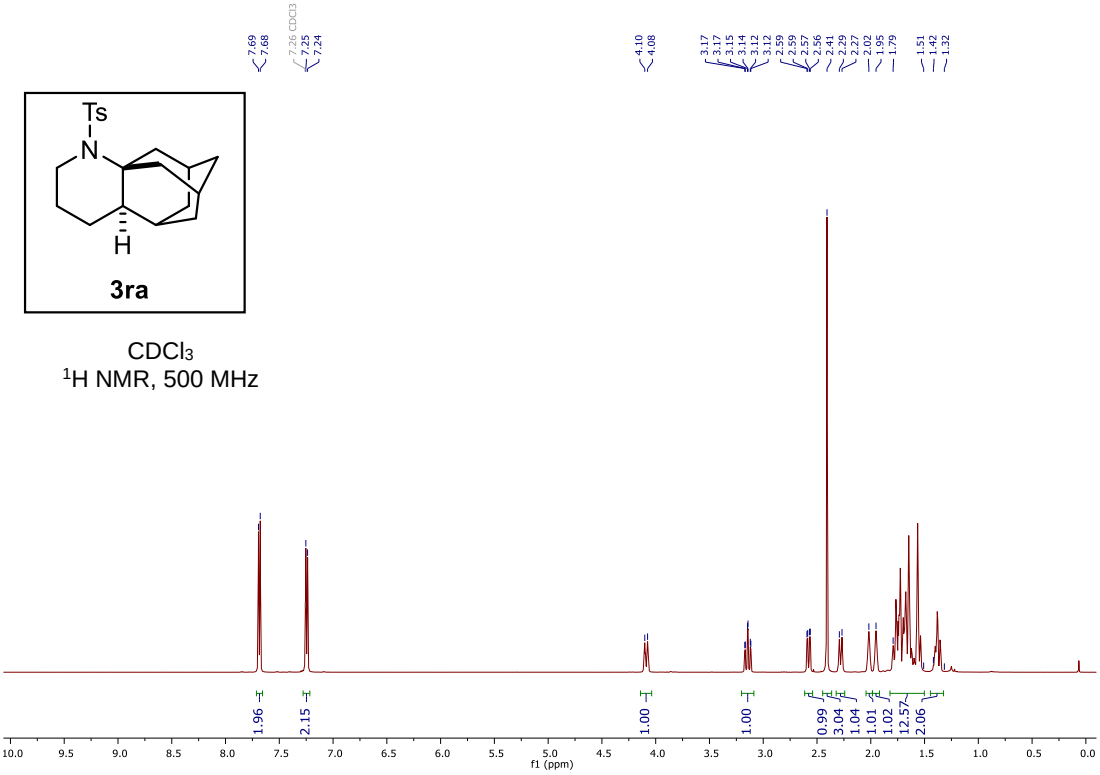
$CDCl_3$
^{13}C NMR, 126 MHz



$CDCl_3$
^{13}C NMR, 126 MHz

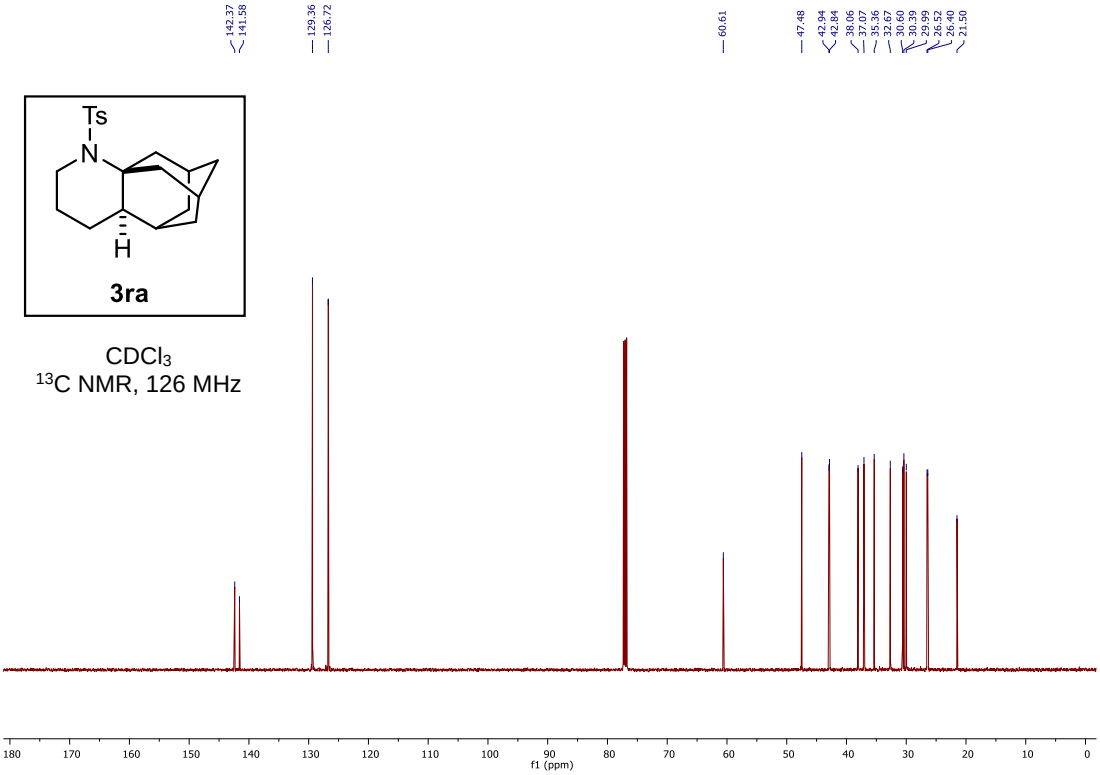
3ra

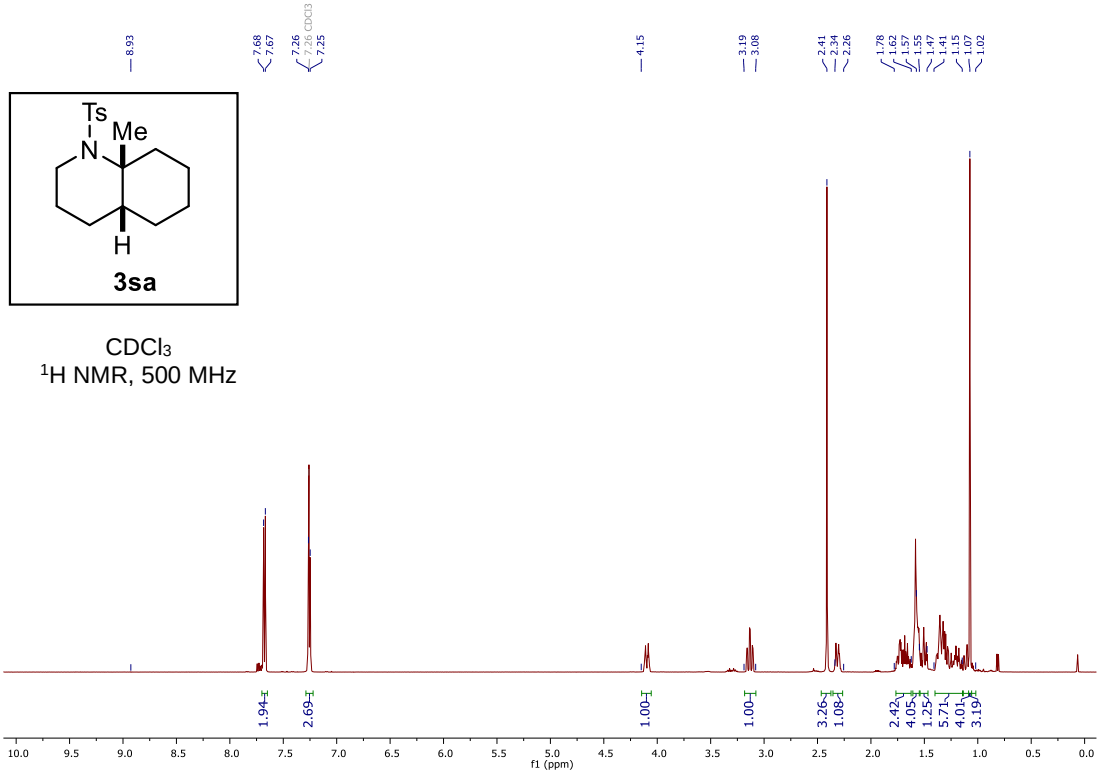
$CDCl_3$
^{1}H NMR, 500 MHz



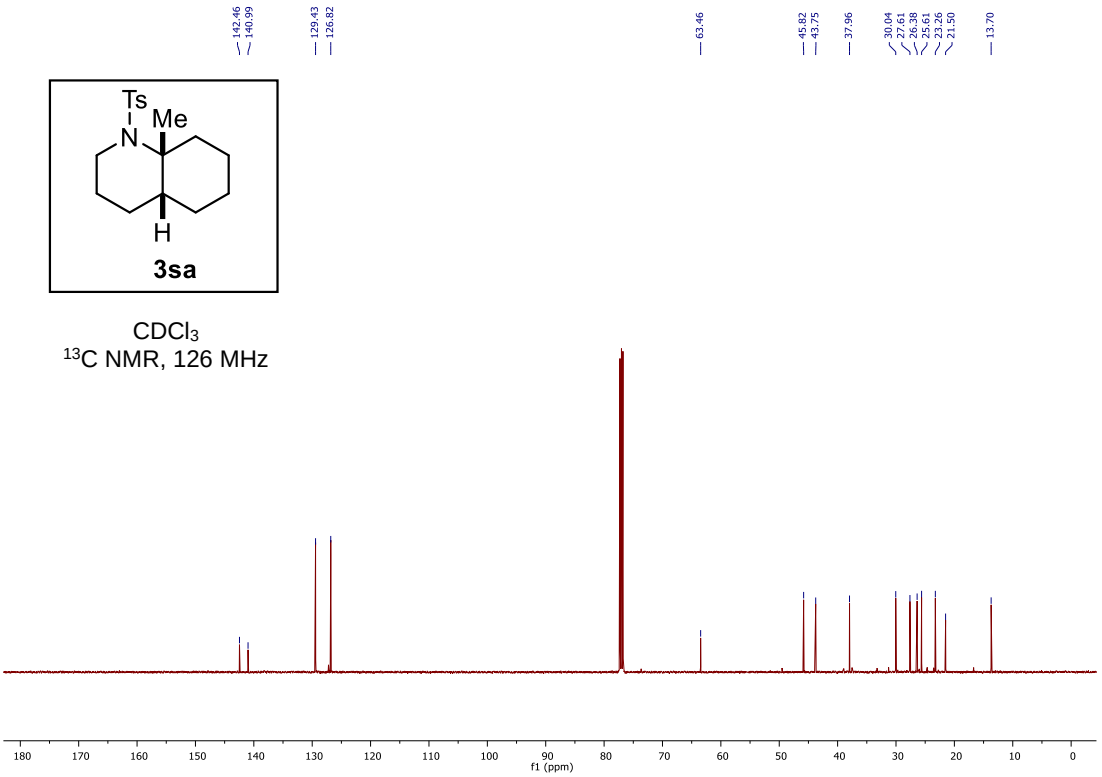
3ra

$CDCl_3$
^{13}C NMR, 126 MHz





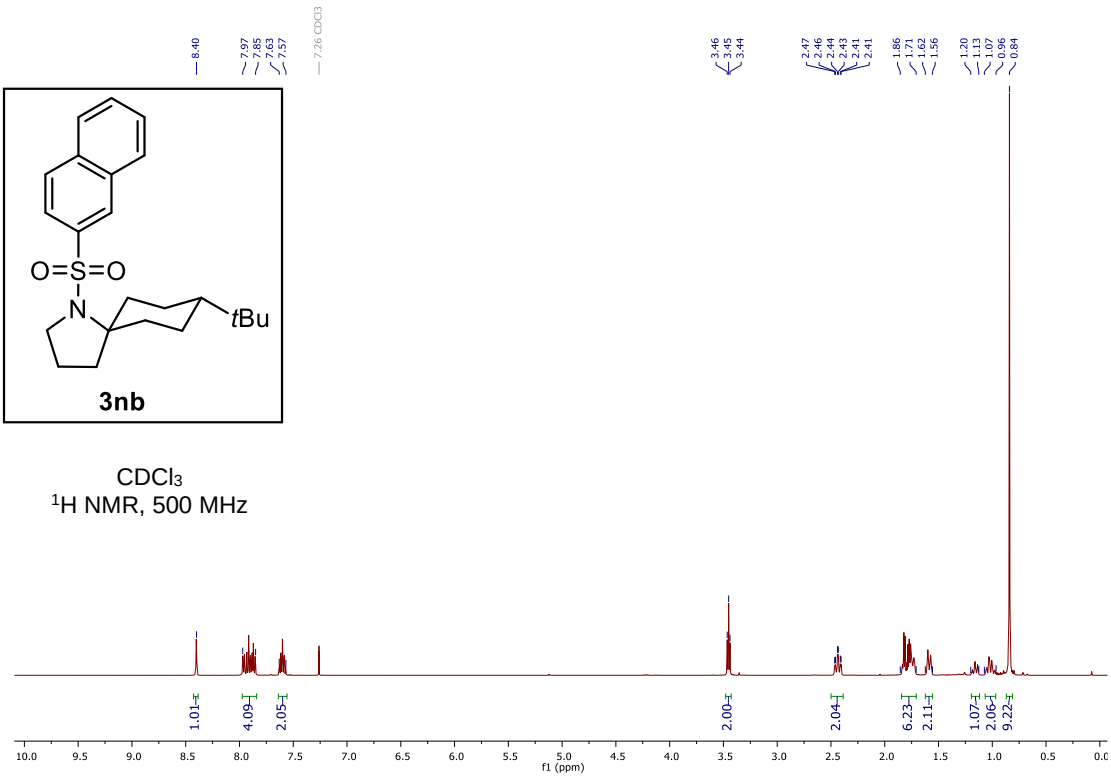
$CDCl_3$
^{1}H NMR, 500 MHz



$CDCl_3$
^{13}C NMR, 126 MHz

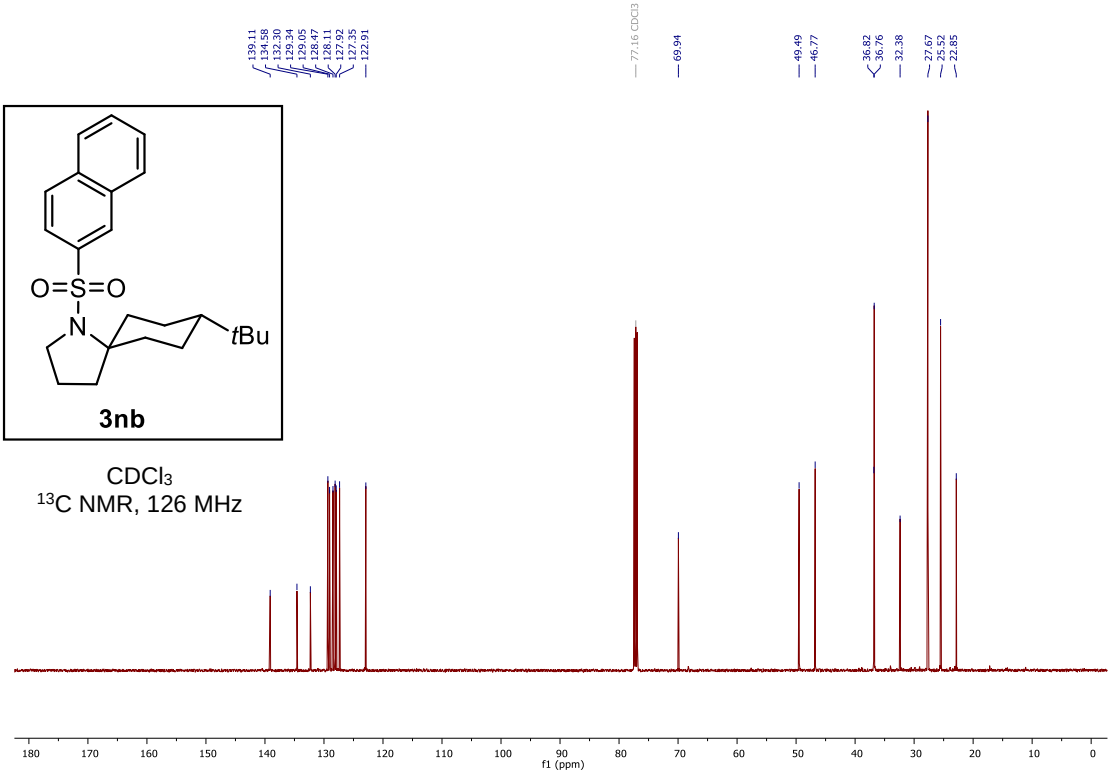
3nb

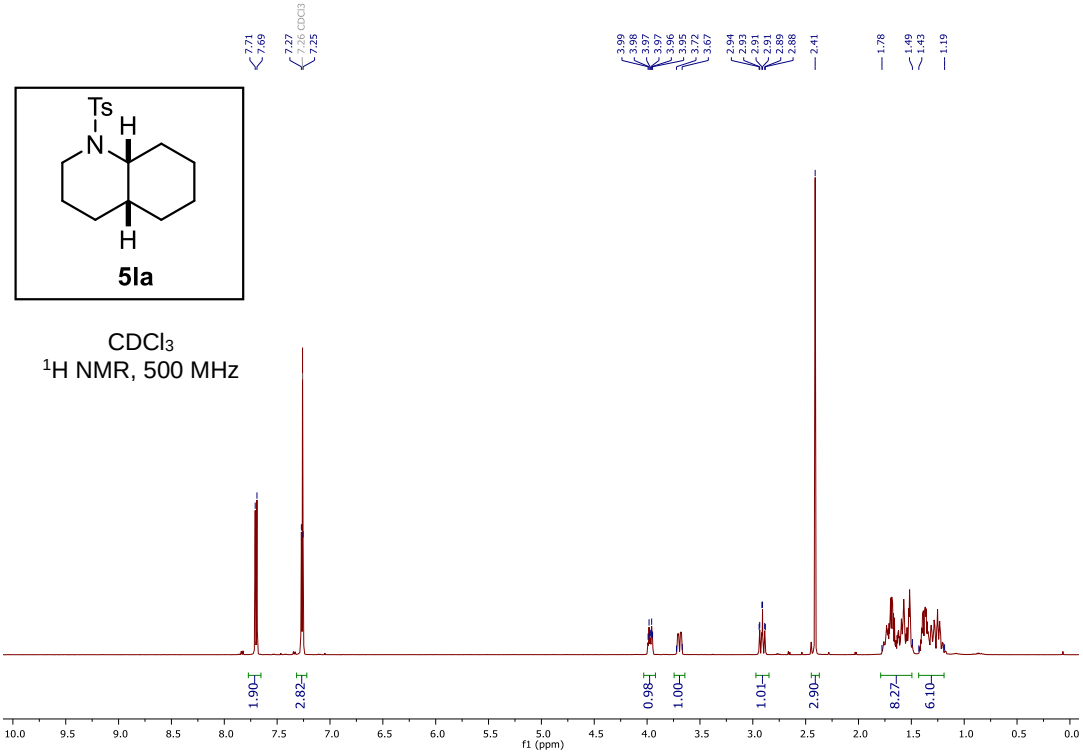
$CDCl_3$
^{1}H NMR, 500 MHz



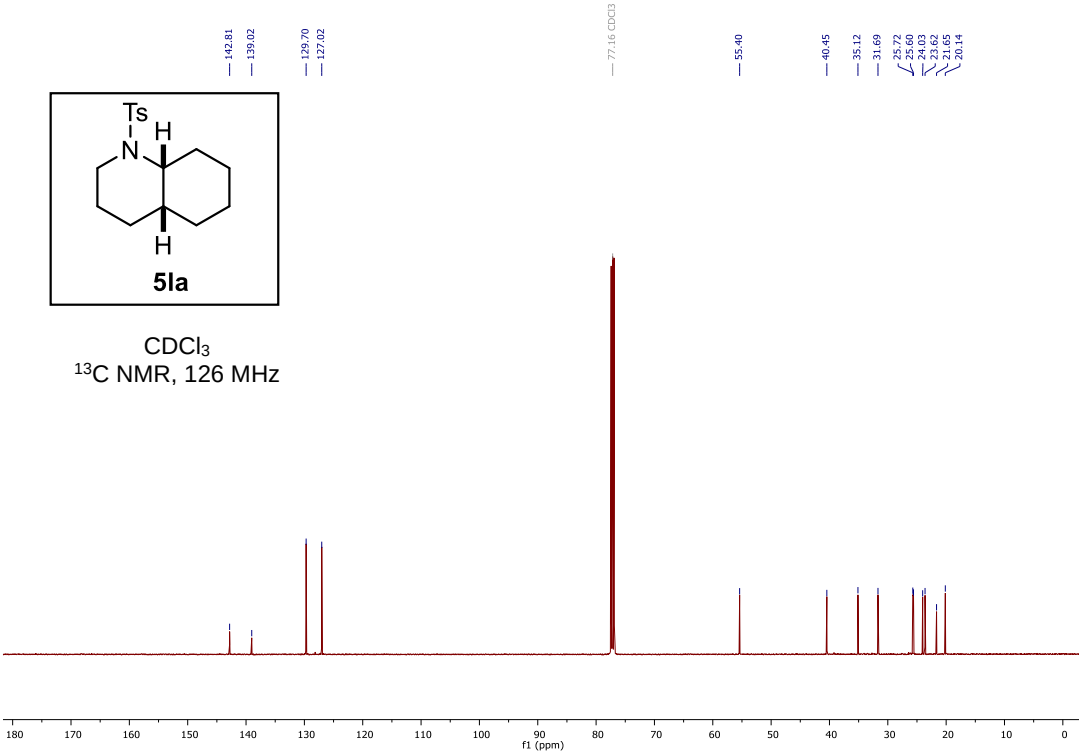
3nb

$CDCl_3$
^{13}C NMR, 126 MHz





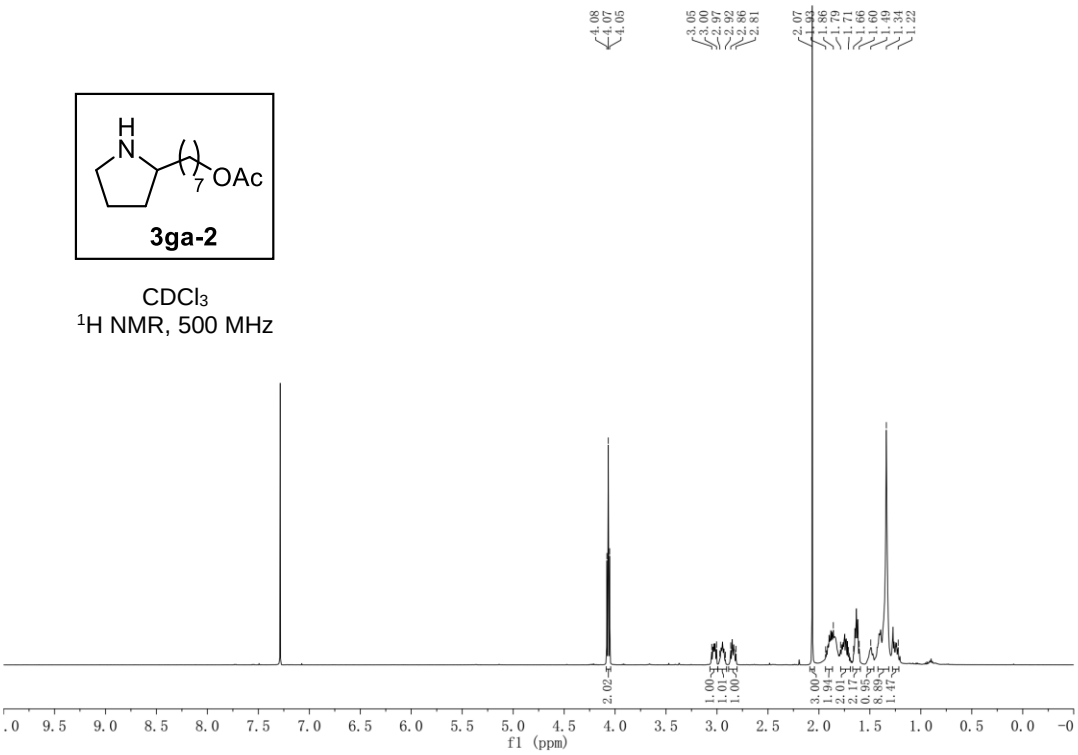
$CDCl_3$
^{1}H NMR, 500 MHz



$CDCl_3$
^{13}C NMR, 126 MHz

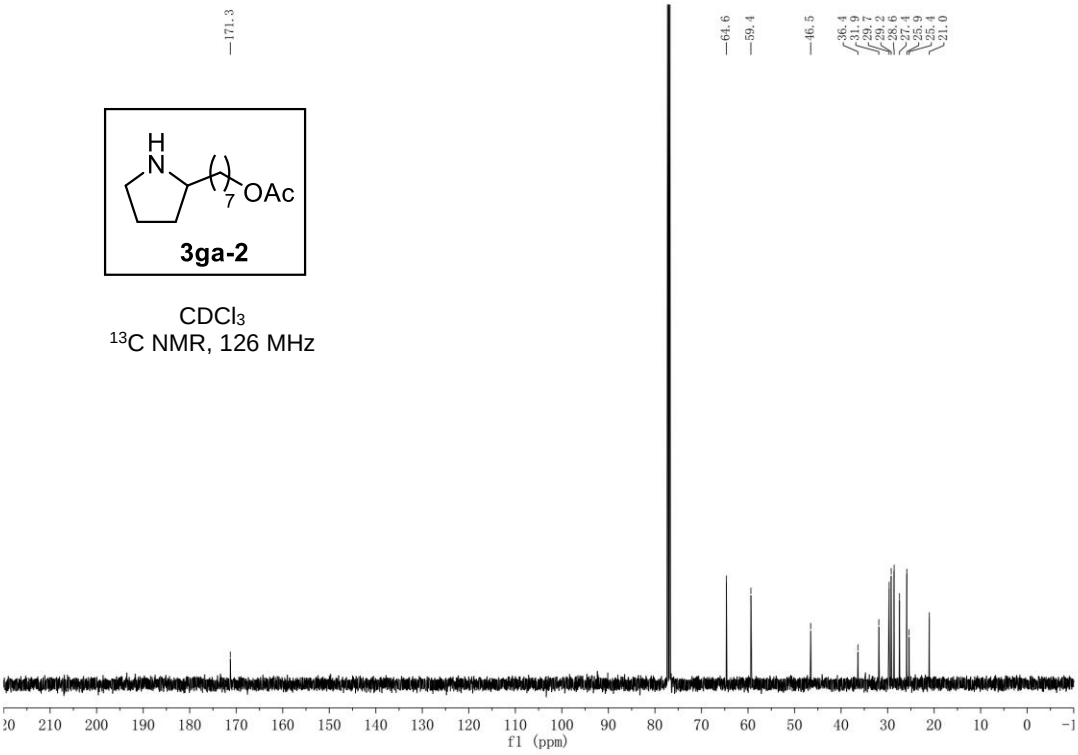
3ga-2

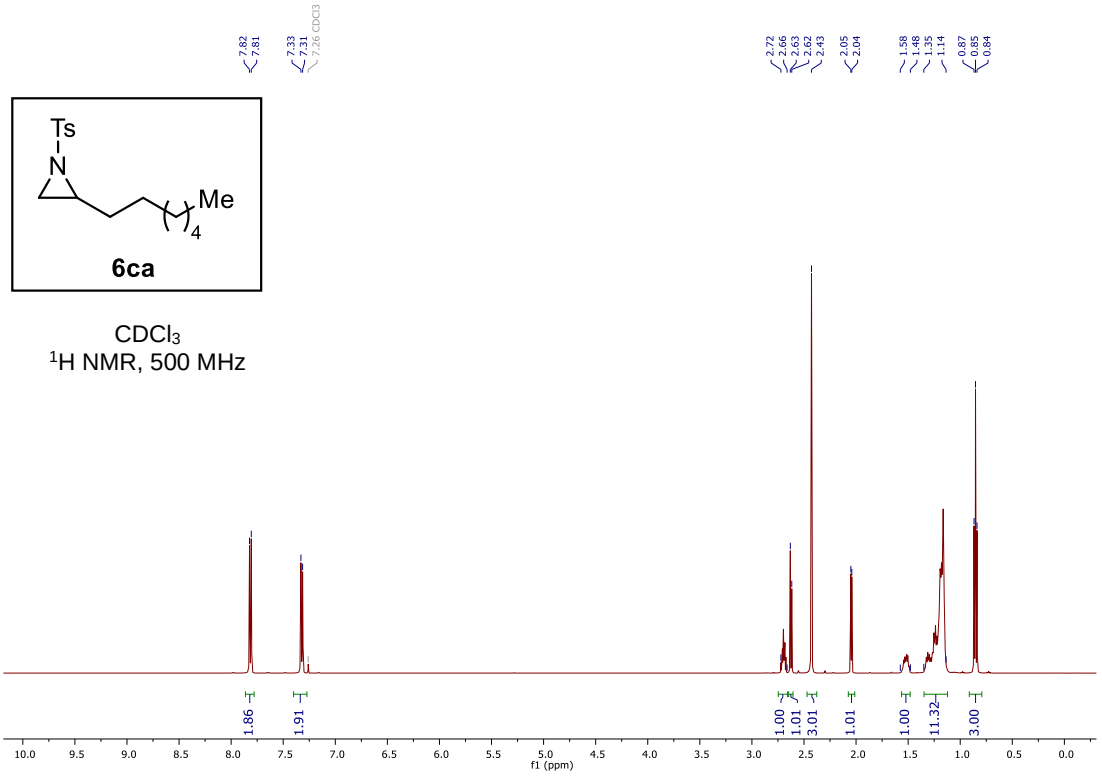
$CDCl_3$
^{1}H NMR, 500 MHz

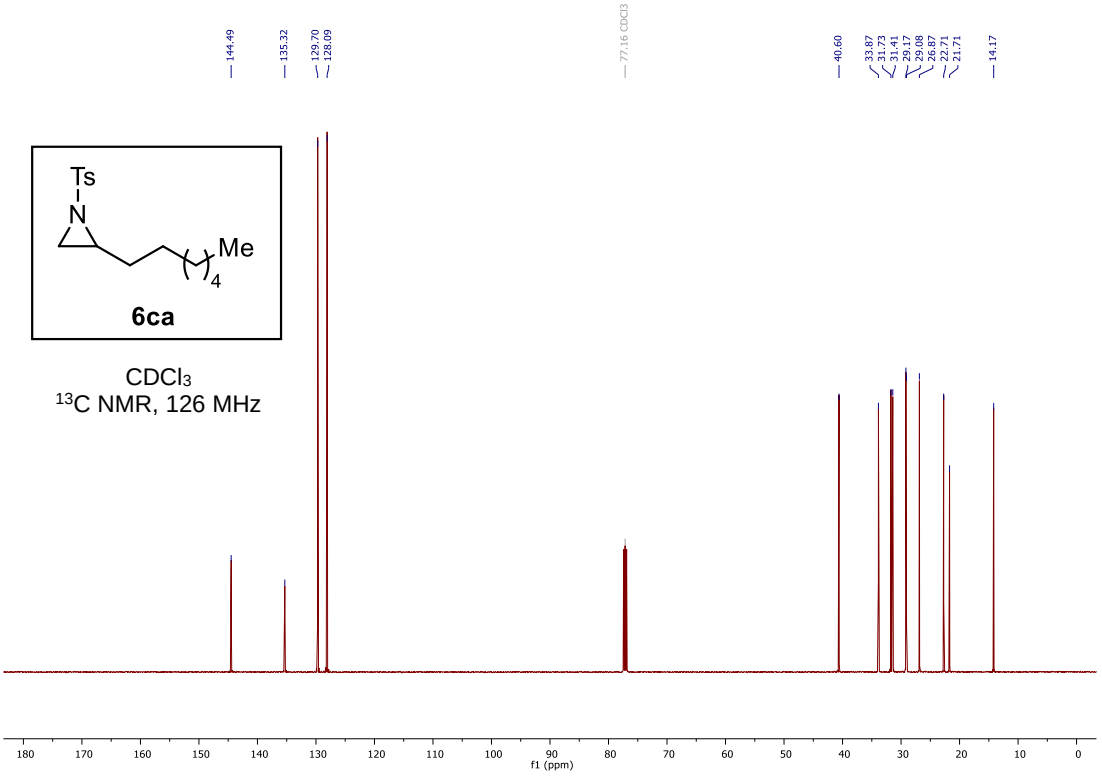


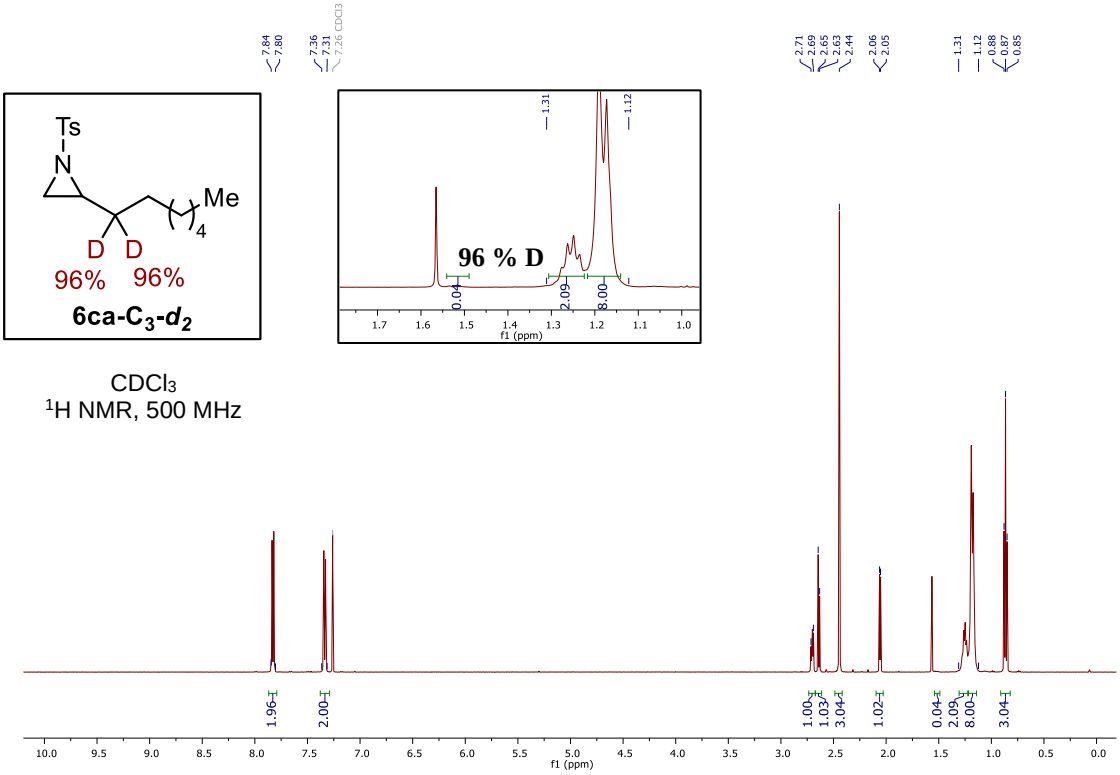
3ga-2

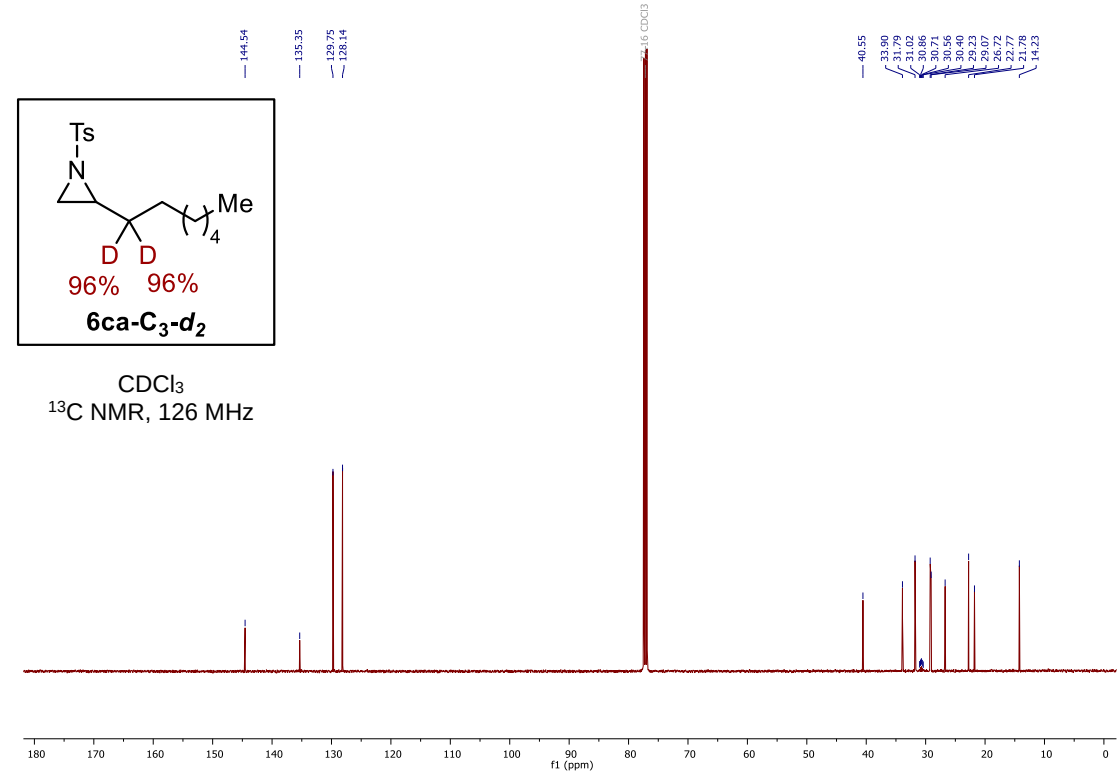
$CDCl_3$
^{13}C NMR, 126 MHz

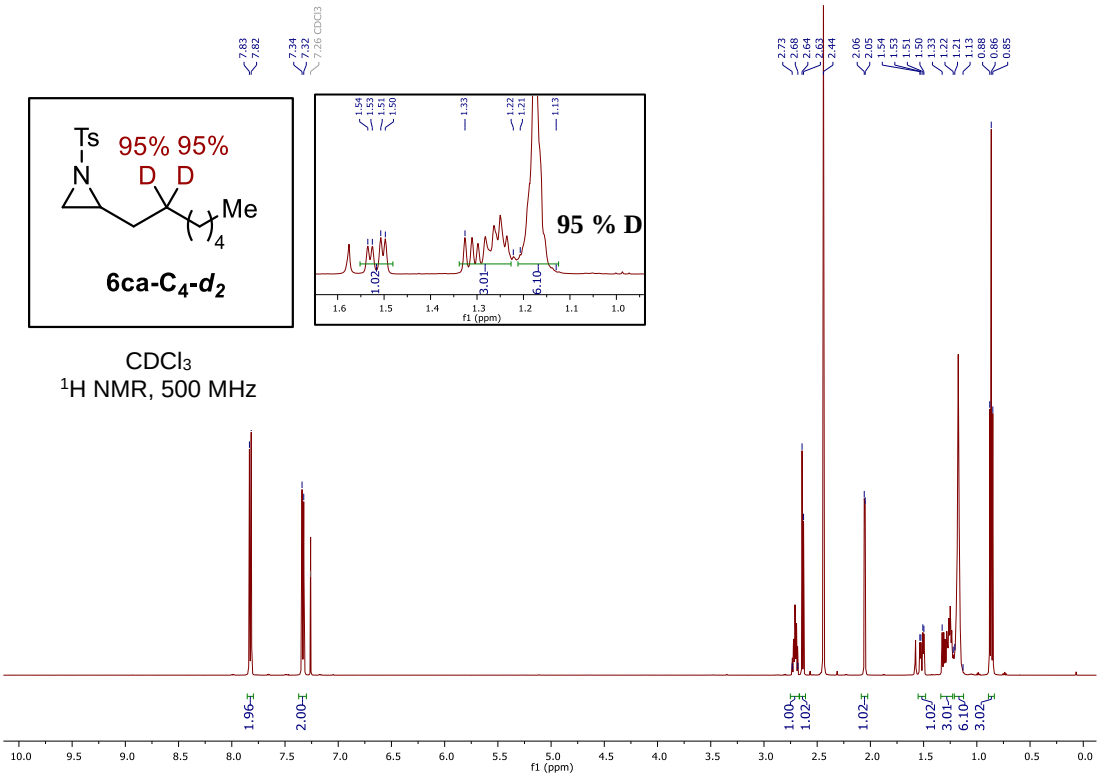


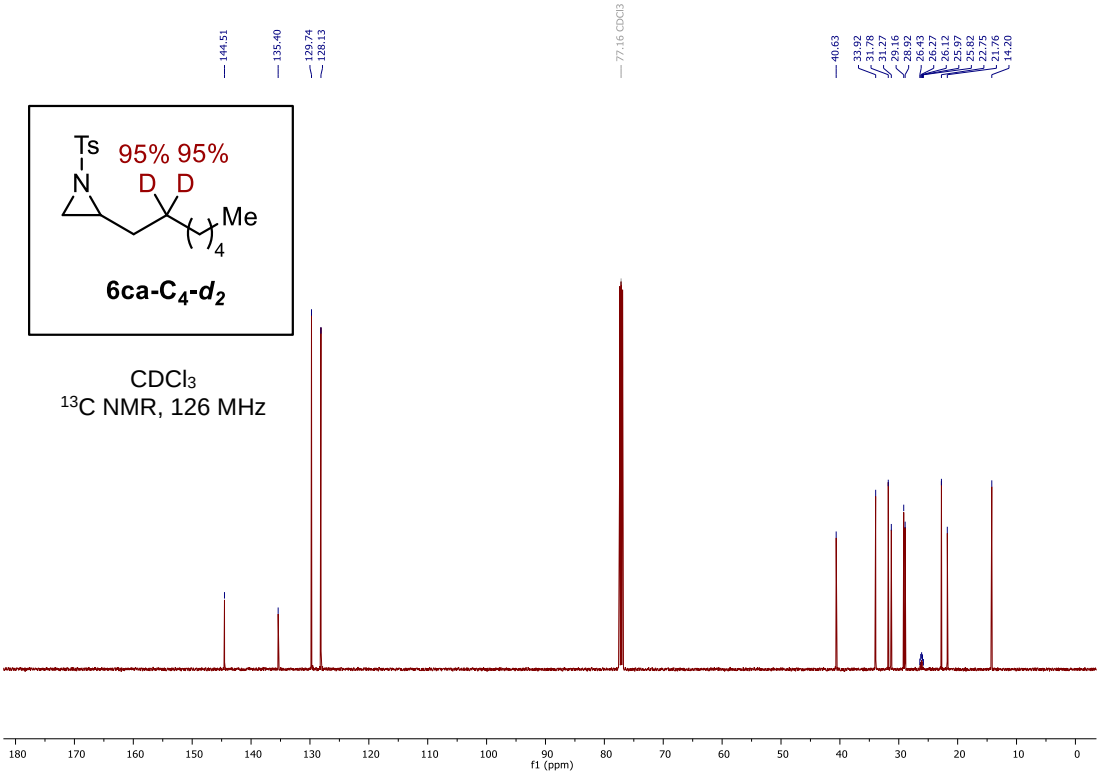

Ts
N
Me
4
6ca
CDCl3
1H NMR, 500 MHz
7.82
7.81
7.33
7.31
7.26 CDCl3
2.72
2.66
2.63
2.62
2.43
2.05
2.04
1.58
1.48
1.35
1.14
0.87
0.85
0.84
1.86
1.91
1.00
1.01
3.01
1.01
1.00
11.32
3.00
f1 (ppm)

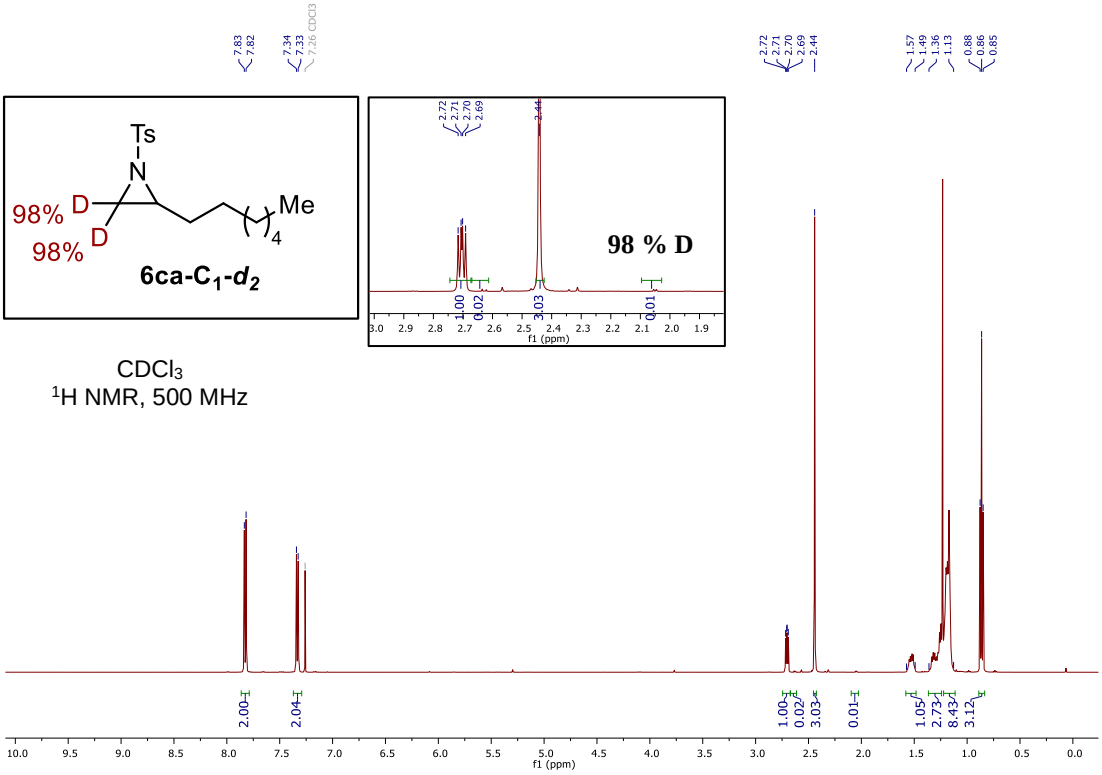

Ts
N
Me
4
6ca
CDCl3
13C NMR, 126 MHz
144.49
135.32
129.70
128.09
77.16 CDCl3
40.60
33.87
31.73
31.41
29.17
29.08
26.87
22.71
21.71
14.17
f1 (ppm)

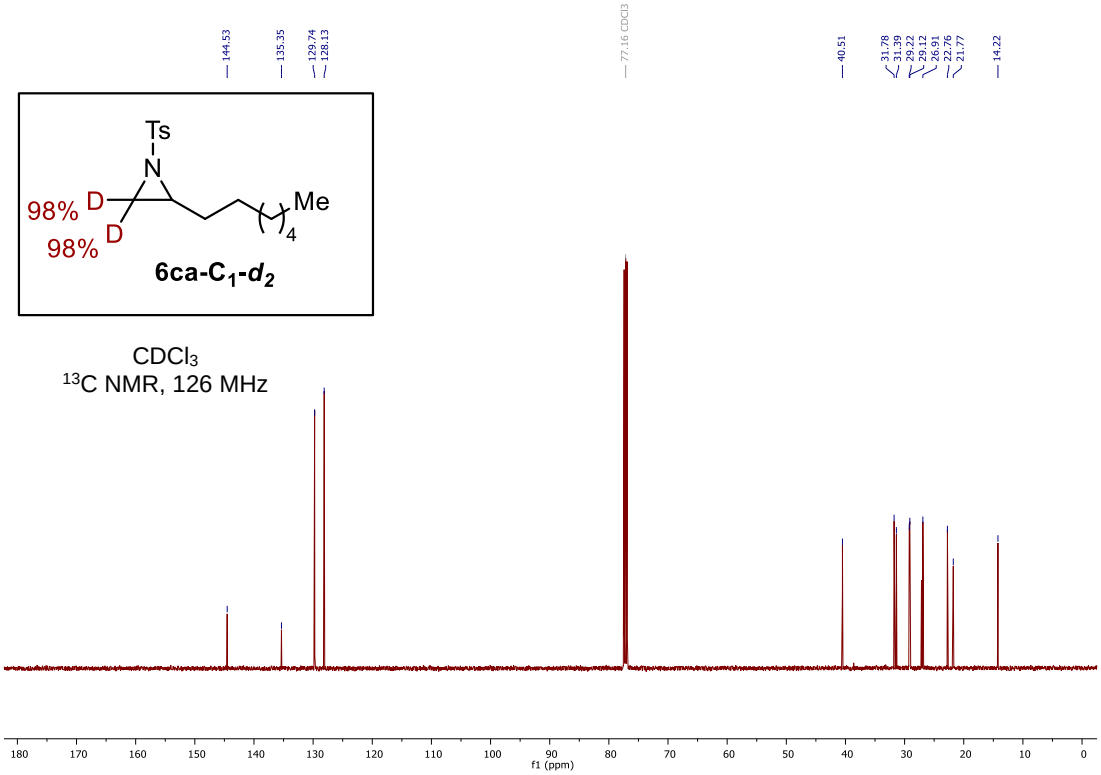

Ts
N
Me
4
D D
96% 96%
6ca-C3-d2
96 % D
CDCl3
1H NMR, 500 MHz
f1 (ppm)

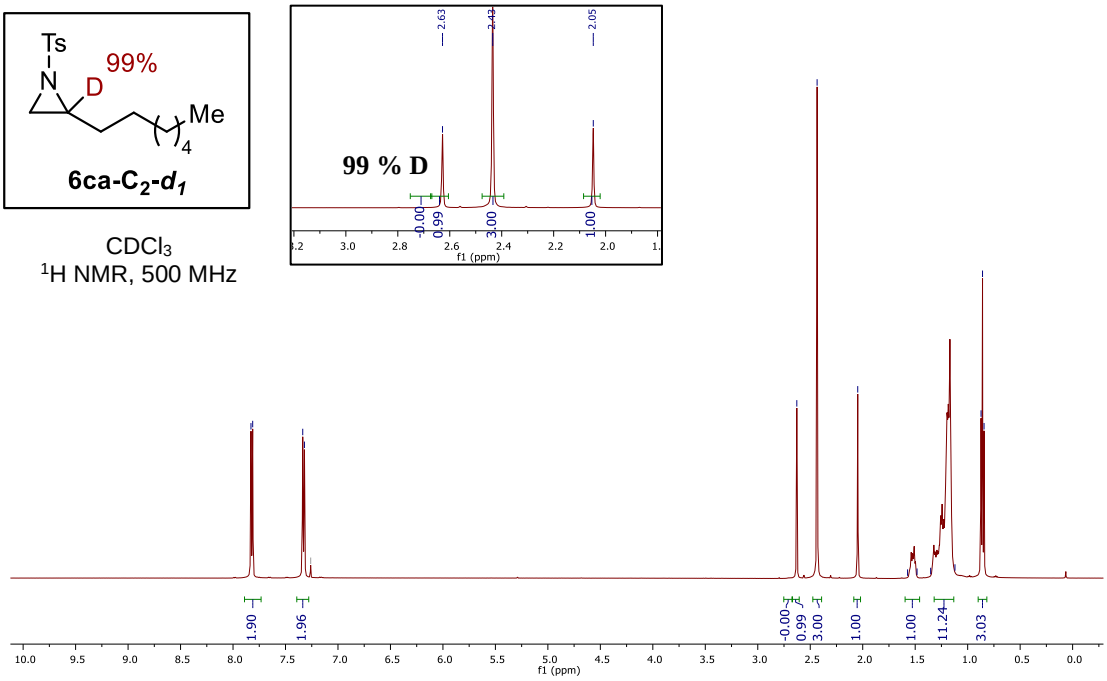

Ts
N
Me
4
D D
96% 96%
6ca-C3-d2
CDCl3
13C NMR, 126 MHz
f1 (ppm)

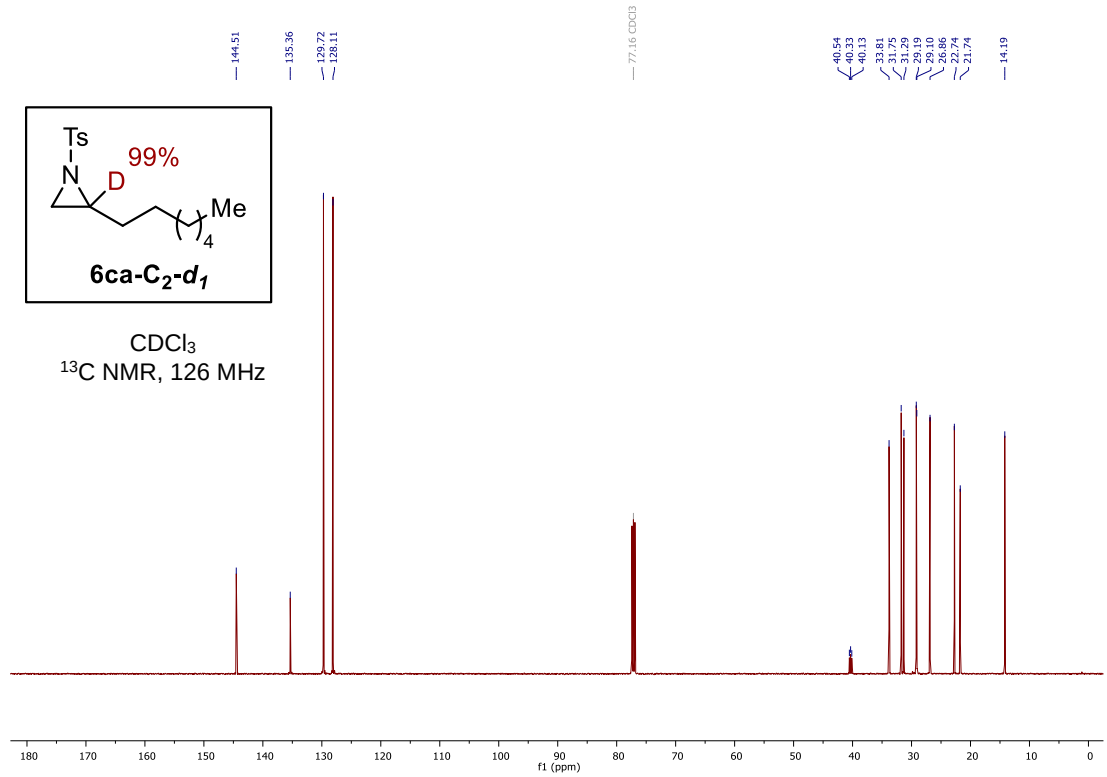

Ts
N
95% 95%
D D
Me
4
6ca-C4-d2
95 % D
CDCl3
1H NMR, 500 MHz
f1 (ppm)


Ts
N
95% 95%
D D
Me
4
6ca-C4-d2
CDCl3
13C NMR, 126 MHz
f1 (ppm)


Ts
N
98% D
98% D
Me
4
6ca-C1-d2
98 % D
CDCl3
1H NMR, 500 MHz
f1 (ppm)


Ts
N
98% D
98% D
Me
4
6ca-C1-d2
CDCl3
13C NMR, 126 MHz
f1 (ppm)


Ts
N
D
99%
Me
4
6ca-C2-d1
CDCl3
1H NMR, 500 MHz
99 % D
f1 (ppm)


Ts
N
D
99%
Me
4
6ca-C2-d1
CDCl3
13C NMR, 126 MHz
f1 (ppm)

Appendix B

SUPPLEMENTARY DATA FOR CHAPTER THREE

Direct Regio- and Diastereoselective Synthesis of δ-Lactams from Acrylamides and Unactivated Alkenes Initiated by RhIII-Catalyzed C−H Activation

Author: Sumin Lee, Natthawat Semakul, Tomislav Rovis
Publication: Angewandte Chemie International Edition
Publisher: John Wiley and Sons
Date: Feb 11, 2020

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Licensed Content Title	Direct Regio- and Diastereoselective Synthesis of δ-Lactams from Acrylamides and Unactivated Alkenes Initiated by RhIII-Catalyzed C−H Activation
Licensed Content Author	Sumin Lee, Natthawat Semakul, Tomislav Rovis
Licensed Content Date	Feb 11, 2020
Licensed Content Volume	59
Licensed Content Issue	12
Licensed Content Pages	5
Type of use	Dissertation/Thesis
Requestor type	Author of this Wiley article
Format	Print and electronic
Portion	Full article
Will you be translating?	No
Title	Ph.D. Dissertation
Institution name	Columbia University
Expected presentation date	May 2021
Requestor Location	Sumin Lee 535 west 111th street apt 35B NEW YORK, NY 10025

Supporting Information

Direct Regio- and Diastereoselective Synthesis of δ-Lactams from Acrylamides and Unactivated Alkenes Initiated by Rh(III)-catalyzed C-H Activation

Sumin Lee, Natthawat Semakul and Tomislav Rovis*

Department of Chemistry, Columbia University, New York, New York 10027

Contents

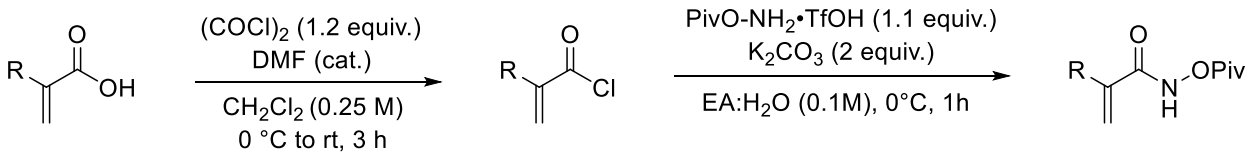
1. General Information

All reactions were carried out using oven-dried glassware with magnetic stirring unless otherwise noted. Anhydrous solvents and reagents were purchased from commercial sources and used without further purification. Flash chromatography was conducted either manually on SiliCycle® SilicaFlash® P60 (230-400 mesh) silica gel or automatically *via* a Teledyne Isco Lumen CombiFlash with RediSep Rf Disposable Flash columns. Thin layer chromatography (TLC) was performed on Silicycle 250μm silica gel 60 Å plates. Visualization was accomplished with UV light (254 nm) and $KMnO_4$. ^1H, ^{19}F NMR and ^{13}C NMR spectra were collected at ambient temperature on Bruker 400 MHz and Bruker Avance III 500 MHz spectrometers unless otherwise noted. Chemical shifts (δ) are reported in parts per million (ppm), coupling constants (J) are reported in Hz, and multiplicity is described using the following abbreviations: singlet (s), multiplet (m), doublet (d), triplet (t), quartet (q), or combinations thereof. ^1H NMR spectra were referenced to 7.26 ppm ($CHCl_3$). ^{13}C NMR spectra were referenced to 77.16 ppm ($CDCl_3$) and all peaks given are singlet unless otherwise noted. Regioisomeric ratios were measured by integration of ^1H NMR spectra of product mixtures prior to purification. High resolution mass spectra (HRMS) were obtained from Columbia University Mass Spectrometry Facility on a JOEL JMSHX110HF mass spectrometer using ASAP ionization model. Infrared spectra were collected on a Perkin Elmer Spectrum Two FT-IR Spectrometer.

2. Preparation of Starting Materials

2a, **2b**, **2c**, **2d, 2e**, **2f**, **2j, 2k, 2l, 2m**, **2n, 2o, 2p, 2q, 2r, 2s, 2t, 2u, 2v** and **2w** were purchased from Sigma Aldrich and used without further purification. **2g,**[1] **2h,**[2] and **2i**[3] were synthesized following literature procedures. Acrylamides (**1a – 1i**) were synthesized following general procedures below.

General Procedure: synthesis of acrylamides



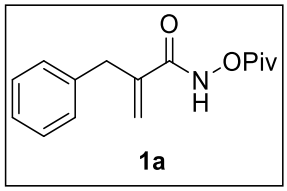
Oxalyl chloride (1.2 equiv.) and catalytic amount of DMF were added dropwise at 0 °C to a solution of acrylic acid (1.5 equiv.) in CH_2Cl_2 (0.25 M). The reaction mixture was warmed to room temperature and

stirred for 3 hours. After completion, volatiles were removed by rotary evaporator and crude material was used without further purification.

PivO-NH_2·TfOH (1.1 equiv.)[4] was dissolved in 0.1 M of ethyl acetate/H_2O 2:1 biphasic mixture. K_2CO_3 was added to the solution and cooled to 0 °C. The corresponding acid chloride was added dropwise to the mixture and stirred for 1 hour at 0 °C. After completion of the reaction, the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate) to afford the corresponding *N*-(pivaloyloxy)acrylamides (**1a**-**k**).

For the synthesis of **1f**, **1g,** and **1h**, the first step was conducted in THF. After full conversion of acid, the crude material was taken without concentration.

2-benzyl-N-(pivaloyloxy)acrylamide (**1a**)



1a

Prepared according to general procedure from commercially available 2-benzylacrylic acid (2.00 g, 12.3 mmol).

Yield: 82%, 2.62 g (over 2 steps), white solid.

$\mathbf{R_f}$ = 0.47 (EA/Hex 1:4).

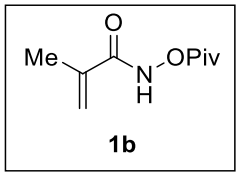
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.36 – 7.29 (m, 2H), 7.28 – 7.19 (m, 3H), 5.93 (s, 1H), 5.39 – 5.34 (m, 1H), 3.67 (s, 2H), 1.31 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.9, 167.1, 141.2, 137.6, 129.1, 128.9, 127.0, 122.6, 38.5, 38.2, 27.1.

IR ($CDCl_3$, cm^{-1}) *v* 3231, 2977, 2252, 1777, 1674, 1625, 1480, 1455, 1269, 1081, 1032, 906, 729, 703, 648.

HRMS (ASAP) m/z $[C_{15}H_{20}NO_3]^+$ ($[M+H]^+$) calculated 262.1443, found 262.1445.

N-(pivaloyloxy)methacrylamide (**1b**)



1b

Prepared according to general procedure from commercially available methacryloyl chloride (260 mg, 2.49 mmol).

Yield: 75%, 345 mg, white solid.

$\mathbf{R_f}$ = 0.38 (EA/Hex 1:4).

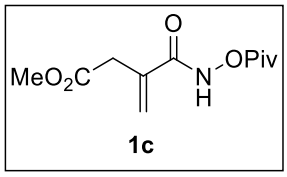
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (s, 1H), 5.84 – 5.80 (m, 1H), 5.50 – 5.45 (m, 1H), 1.99 – 19.7 (m, 3H), 1.32 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.1, 167.4, 137.1, 122.1, 38.5, 27.1, 18.4.

IR ($CDCl_3$, cm^{-1}) *v* 3222, 2977, 2936, 2253, 1776, 1677, 1629, 1480, 1457, 1081, 905, 727, 648.

HRMS (ASAP) m/z $[C_9H_{16}NO_3]^+$ ($[M+H]^+$) calculated 186.1130, found 186.1130.

methyl 3-((pivaloyloxy)carbamoyl)but-3-enoate (**1c**)



1c

Prepared according to general procedure from 4-methoxy-2-methylene-4-oxobutanoic acid[5] (432 mg, 3.00 mmol).

Yield: 65%, 471 mg (over 2 steps), colorless liquid.

$\mathbf{R_f}$ = 0.13 (EA/Hex 1:4).

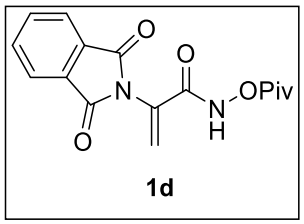
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (s, 1H), 6.05 (s, 1H), 5.61 (s, 1H), 3.72 (s, 3H), 3.39 (s, 2H), 1.32 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6, 171.5, 166.5, 134.7, 125.5, 52.6, 38.5, 37.9, 27.2.

IR ($CDCl_3$, cm^{-1}) *v* 3255, 2977, 2876, 2255, 1777, 1735, 1680, 1632, 1480, 1268, 1203, 1080, 1035, 909, 727, 647.

HRMS (ASAP) m/z $[C_{11}H_{18}NO_5]^+$ ($[M+H]^+$) calculated 244.1185, found 244.1183.

2-(1,3-dioxoisoindolin-2-yl)-N-(pivaloyloxy)acrylamide (**1d**)



1d

Prepared according to general procedure from 2-(1,3-dioxoisoindolin-2-yl)acrylic acid[6] (830 mg, 3.82 mmol).

Yield: 45%, 547 mg (over 2 steps), white solid.

$\mathbf{R_f}$ = 0.10 (EA/Hex 1:4).

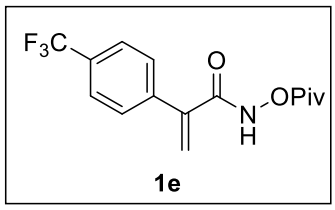
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.93 – 7.88 (m, 2H), 7.81 – 7.74 (m, 2H), 6.35 (d, J = 1.4 Hz, 1H), 5.94 (d, J = 1.4 Hz, 1H), 1.32 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 166.3, 162.0, 134.8, 131.7, 129.9, 124.2, 123.1, 38.6, 27.1.

IR ($CDCl_3$, cm^{-1}) ν 3237, 2976, 2937, 2255, 1785, 1722, 1633, 1480, 1468, 1375, 1288, 1078, 905, 886, 727, 649.

HRMS (ASAP) m/z $[C_{16}H_{17}N_2O_5]^+$ ($[M+H]^+$) calculated 317.1137, found 317.1143.

N-(pivaloyloxy)-2-(4-(trifluoromethyl)phenyl)acrylamide (**1e**)



1e

Prepared according to general procedure from 2-(4-(trifluoromethyl)phenyl)acrylic acid[7] (1.15 g, 5.3 mmol).

Yield: 60%, 1.00 g (over 2 steps), white solid.

$\mathbf{R_f}$ = 0.35 (EA/Hex 1:4).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.66 (m, 2H), 7.60 (m, 2H), 6.21 (s, 1H), 5.88 (s, 1H), 1.34 (s, 9H).

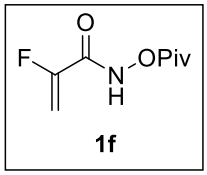
^{13}C NMR (126 MHz, $CDCl_3$) δ 176.9, 165.7, 140.8, 139.2, 131.1 (q, J = 32.8 Hz), 128.3, 125.9 (q, J = 3.8 Hz), 124.5, 124.0 (q, J = 272.1 Hz), 38.6, 27.1.

^{19}F NMR (471 MHz, $CDCl_3$) δ -61.92.

IR ($CDCl_3$, cm^{-1}) ν 3196, 2977, 1781, 1669, 1615, 1481, 1407, 1325, 1168, 1122, 1068, 904, 849, 727, 649.

HRMS (ASAP) m/z $[C_{15}H_{17}F_3NO_3]^+$ ($[M+H]^+$) calculated 316.1161, found 316.1144.

2-fluoro-*N*-(pivaloyloxy)acrylamide (**1f**)



1f

Prepared according to general procedure from commercially available 2-fluoroacrylic acid (233 mg, 2.59 mmol).

Yield: 65%, 320 mg (over 2 steps), white solid.

$\mathbf{R_f}$ = 0.39 (EA/Hex 1:4).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.48 (s, 1H), 5.75 (dd, J = 47.0, 3.7 Hz, 1H), 5.24 (dd, J = 15.5, 3.7 Hz, 1H), 1.33 (s, 9H)

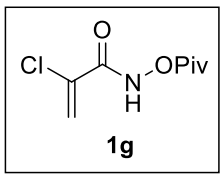
^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 157.2 (d, J = 31.8 Hz), 154.6 (d, J = 268.4 Hz), 101.2 (d, J = 13.1 Hz), 38.6, 27.1.

^{19}F NMR (282 MHz, $CDCl_3$) δ -122.1 (dd, J = 47.0, 15.5 Hz).

IR ($CDCl_3$, cm^{-1}) ν 3227, 2978, 2939, 2256, 1787, 1693, 1662, 1481, 1301, 1203, 1072, 1042, 944, 904, 728, 634.

HRMS (ASAP) m/z $[C_8H_{13}FNO_3]^+$ ($[M+H]^+$) calculated 190.0879, found 190.0884.

2-chloro-*N*-(pivaloyloxy)acrylamide (**1g**)



1g

Prepared according to general procedure from commercially available 2-chloroacrylic acid (300 mg, 2.82 mmol).

Yield: 49%, 283 mg (over 2 steps), white solid.

$\mathbf{R_f}$ = 0.41 (EA/Hex 1:4).

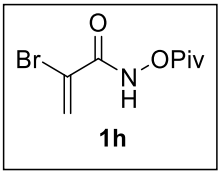
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (s, 1H), 6.64 (d, J = 1.7 Hz, 1H), 5.89 (d, J = 1.7 Hz, 1H), 1.34 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 158.7, 129.2, 125.0, 38.6, 27.1.

IR ($CDCl_3$, cm^{-1}) ν 3222, 2976, 2938, 1785, 1678, 1612, 1479, 1369, 1268, 1144, 1070, 941, 868, 764.

HRMS (ESI+APCI) m/z $[C_8H_{13}ClNO_3]^+$ ($[M+H]^+$) calculated 206.0584, found 206.0586.

2-bromo-*N*-(pivaloyloxy)acrylamide (**1h**)



1h

Prepared according to general procedure from commercially available 2-bromoacrylic acid (300 mg, 1.98 mmol).

Yield: 25%, 124 mg (over 2 steps), white solid.

$\mathbf{R_f}$ = 0.47 (EA/Hex 1:4).

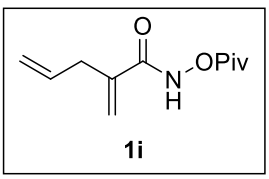
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.07 (d, J = 1.8 Hz, 1H), 6.14 (d, J = 1.9 Hz, 1H), 1.34 (s, 9H),

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 158.9, 129.8, 118.2, 38.6, 27.11.

IR ($CDCl_3$, cm^{-1}) ν 3219, 2975, 2935, 1782, 1677, 1605, 1478, 1462, 1369, 1267, 1132, 1069, 1031, 942, 868, 717.

HRMS (ASAP) m/z $[C_8H_{13}BrNO_3]^+$ ($[M+H]^+$) calculated 250.0079, found 250.0077.

2-methylene-*N*-(pivaloyloxy)pent-4-enamide (**1i**)



1i

Prepared according to general procedure from 2-methylenepent-4-enoic acid[8] (540 mg, 4.81 mmol).

Yield: 74%, 750 mg (over 2 steps), white solid.

$\mathbf{R_f}$ = 0.50 (EA/Hex 1:4).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (s, 1H), 5.93 (s, 1H), 5.85 (ddt, *J* = 17.0, 10.4, 6.6 Hz, 1H), 5.50 (m, 1H), 5.24 – 5.14 (m, 2H), 3.13 – 3.07 (m, 2H), 1.33 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.0, 167.0, 139.8, 134.6, 122.5, 118.1, 38.5, 36.3, 27.1.

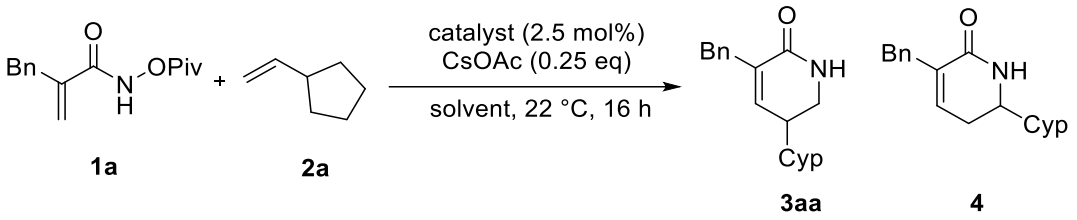
IR ($CDCl_3$, cm^{-1}) *v* 3223, 2977, 2937, 2875, 1777, 1672, 1625, 1480, 1368, 1227, 1081, 906, 729, 648.

HRMS (ASAP) m/z $[C_{11}H_{18}NO_3]^+$ ($[M+H]^+$) calculated 212.1287, found 212.1290.

Synthesis of $[Cp^tRhCl_2]_2$ catalyst

To a solution of di-*tert*-butylcyclopentadiene (0.48 mmol, 1.25 equiv.) and $RhCl_3 \cdot 3H_2O$ (100 mg, 0.38 mmol, 1.0 equiv.) in MeOH (1.9 mL) were added a few drops of water. The reaction mixture was stirred at 65 °C for a period of 4 days. The reaction mixture was cooled to 22 °C, and the precipitate was collected by vacuum filtration and rinsed successively with cold ethanol and pentane. The solid was then dissolved in methylene chloride and the resultant solution was filtered through a plug of celite. The volatiles were evaporated under reduced pressure to obtain the desired $[Cp^tRhCl_2]_2$ complex. **Yield**: 40%, 53.5 mg. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.66 (d, *J* = 1.5 Hz, 2H), 5.37 (t, *J* = 1.5 Hz, 1H), 1.35 (s, 18H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 108.82 (d, J = 9.5 Hz), 82.59 (d, J = 8.0 Hz), 81.38 (d, J = 8.0 Hz), 31.1, 30.2. **IR** ($CDCl_3$, cm^{-1}) *v* 3061, 2960, 2908, 2871, 1671, 1620, 1486, 1464, 1369, 1256, 1167, 905, 856, 730.

3. Detailed Optimization Table



1a **2a** **3aa** **4**

entry	solvent	catalyst	yield of **3aa** (%)[a]	*rr* (**3aa** : **4**)[a]
1	MeOH (0.3 M)	$[Cp^*RhCl_2]_2$	32	1 : 1.6
2	HFIP (0.3 M)	$[Cp^*RhCl_2]_2$	34	1 : 1.1
3	TFE (0.3 M)	$[Cp^*RhCl_2]_2$	38	1 : 1.1
4	MeOH (0.3 M)	$[Cp^tRhCl_2]_2$	50	13.6 : 1
5	HFIP (0.3 M)	$[Cp^tRhCl_2]_2$	54	8.7 : 1
6	**TFE (0.3 M)**	**$[Cp^tRhCl_2]_2$**	**82**	**10.2 : 1**
7	TFE (0.3 M)	$[Cp^{*CF3}RhCl_2]_2$	12	4.0 : 1
8	TFE (0.3 M)	$[Cp^{*tBu}RhCl_2]_2$	63	3.4 : 1
9	TFE (0.3 M)	$[Ind^*RhCl_2]_2$	< 5	-
10	TFE (0.3 M)	$[Cp^{*2,6\text{-}dFPh}RhCl_2]_2$	63	4.2 : 1
11	TFE (0.3 M)	$[Cp^{*Ph}RhCl_2]_2$	65	3.0 : 1
12	TFE (0.3 M)	$[Cp^*CoCl_2]_2$	0	-
13	TFE (0.3 M)	$[Cp^*IrCl_2]_2$	0	-

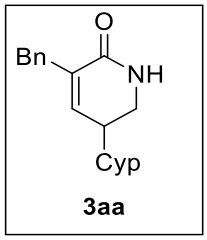
Reactions were conducted on a 0.1 mmol scale using **1a** (1.0 equiv) and **2a** (2.0 equiv). [a]Determined by analysis of ^{1}H NMR of the unpurified reaction mixture. Cp^t = di-*tert*-butylcyclopentadienyl, Cp^{*CF3} = tetramethyl(trifluoromethyl)cyclopentadienyl, Cp^{*tBu} = *tert*-butyltetramethylcyclopentadienyl, Ind* = heptamethylindenyl, $Cp^{*2,6\text{-}dFPh}$ = 2,6-difluorophenyltetramethylcyclopentadienyl, Cp^{*Ph} = phenyltetramethylcyclopentadienyl.

4. General Procedure for δ-Lactam Synthesis

Acrylamide **1** (0.1 mmol, 1 equiv), $[Cp^tRhCl_2]_2$ (0.0025 mmol, 2.5 mol%) were measured in a 1 dram vial with a magnetic stir bar. After the addition of 0.2 mL of trifluoroethanol (TFE) to the vial, alkene coupling partner **2** (0.2 mmol, 2 equiv) and cesium acetate (0.025 mmol, 0.25 equiv) in 0.13 mL of TFE were added. The reaction mixture was stirred at 22 °C for 16 hours and quenched with saturated aqueous solution of $NaHCO_3$ and extracted 3 times with DCM. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solid was filtered and the filtrate was concentrated by rotary evaporator. A crude ^1H NMR spectrum was collected with 1,3,5-trimethoxybenzene as the internal standard. Purification was performed by flash chromatography using ethyl acetate and hexane as the eluent.

5. Product Characterization

3-benzyl-5-cyclopentyl-5,6-dihydropyridin-2(1H)-one (**3aa**)



3aa

Yield: 19.2 mg, 75%, 10.2 : 1 *rr*. off-white solid.

R_f = 0.35 (EA/Hex 1:1).

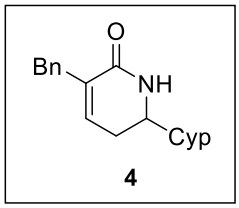
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 2H), 7.24 – 7.16 (m, 3H), 6.15 (d, *J* = 3.7 Hz, 1H), 6.02 (s, 1H), 3.64 (d, *J* = 15.7 Hz, 1H), 3.58 (d, *J* = 15.6 Hz, 1H), 3.40 (ddd, *J* = 12.1, 5.9, 3.1 Hz, 1H), 3.18 (ddd, *J* = 11.7, 8.4, 2.5 Hz, 1H), 2.27 – 2.17 (m, 1H), 1.89 – 1.80 (m, 1H), 1.82 – 1.69 (m, 2H), 1.68 – 1.57 (m, 2H), 1.56 – 1.45 (m, 2H), 1.19 – 1.06 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 140.8, 139.6, 134.2, 129.3, 128.5, 126.2, 44.4, 42.1, 40.1, 36.4, 31.0, 30.3, 25.4, 25.2.

IR ($CDCl_3$, cm^{-1}) *v* 3215, 3061, 3026, 2947, 2865, 1673, 1625, 1476, 1451, 1267, 825, 726, 699.

HRMS (ASAP) m/z $[C_{17}H_{22}NO]^+$ ($[M+H]^+$) calculated 256.1701, found 256.1703.

3-benzyl-6-cyclopentyl-5,6-dihydropyridin-2(1H)-one (**4**)



4

Yield: 10 mg, 39% ($[Cp^*RhCl_2]_2$ was used as a catalyst), 1 : 1.1 *rr*. white solid.

$\mathbf{R_f}$ = 0.56 (EA/Hex 1:1).

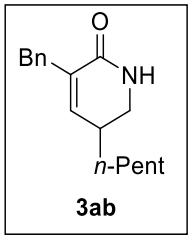
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 2H), 7.23 – 7.16 (m, 3H), 6.09 (ddt, *J* = 6.0, 3.0, 1.6 Hz, 1H), 5.53 (s, 1H), 3.68 – 3.54 (m, 2H), 3.29 (dddd, *J* = 12.0, 8.6, 5.0, 1.0 Hz, 1H), 2.30 (dddd, *J* = 17.4, 6.2, 5.0, 1.3 Hz, 1H), 2.14 (ddq, *J* = 17.3, 11.9, 2.6 Hz, 1H), 1.97 – 1.87 (m, 1H), 1.87 – 1.79 (m, 1H), 1.77 – 1.69 (m, 1H), 1.69 – 1.50 (m, 4H), 1.27 – 1.18 (m, 1H), 1.17 – 1.08 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 139.6, 135.9, 134.9, 129.4, 128.5, 126.3, 56.3, 44.8, 36.1, 29.8, 29.3, 29.2, 25.4, 25.4.

IR ($CDCl_3$, cm^{-1}) *v* 3214, 3062, 3027, 2948, 2868, 1673, 1630, 1452, 1426, 906, 728, 699.

HRMS (ASAP) m/z $[C_{17}H_{22}NO]^+$ ($[M+H]^+$) calculated 256.1701, found 256.1701.

3-benzyl-5-pentyl-5,6-dihydropyridin-2(1H)-one (**3ab**)



3ab

Yield: 19.6 mg, 76%, 9.4 : 1 *rr*. white solid.

$\mathbf{R_f}$ = 0.44 (EA/Hex 1:1).

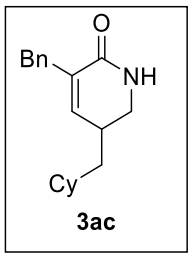
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 2H), 7.24 – 7.16 (m, 3H), 6.09 – 6.05 (m, 1H), 5.96 (s, 1H), 3.64 – 3.57 (m, 2H), 3.40 (ddd, *J* = 12.0, 5.9, 3.1 Hz, 1H), 3.11 (ddd, *J* = 11.6, 8.5, 2.5 Hz, 1H), 2.44 – 2.35 (m, 1H), 1.48 – 1.33 (m, 2H), 1.33 – 1.20 (m, 6H), 0.87 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 141.6, 139.6, 134.0, 129.3, 128.5, 126.2, 44.7, 36.2, 34.6, 32.1, 31.9, 26.7, 22.6, 14.1.

IR ($CDCl_3$, cm^{-1}) *v* 3207, 3061, 3027, 2923, 2854, 1674, 1625, 1477, 1453, 1074, 824, 699.

HRMS (ASAP) m/z $[C_{17}H_{24}NO]^+$ ($[M+H]^+$) calculated 258.1858, found 258.1857.

3-benzyl-5-(cyclohexylmethyl)-5,6-dihydropyridin-2(1H)-one (**3ac**)



3ac

Yield: 20.4 mg, 72%, 6.7 : 1 *rr*. white solid.

$\mathbf{R_f}$ = 0.50 (EA/Hex 1:1).

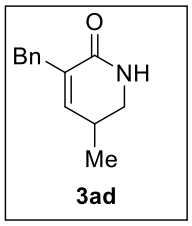
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.24 – 7.16 (m, 3H), 6.08 – 6.02 (m, 1H), 5.54 (s, 1H), 3.60 (s, 2H), 3.39 (ddd, J = 12.1, 5.8, 3.1 Hz, 1H), 3.08 (ddd, J = 11.6, 8.3, 2.6 Hz, 1H), 2.56 – 2.48 (m, 1H), 1.73 – 1.61 (m, 5H), 1.37 – 1.06 (m, 6H), 0.93 – 0.77 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 142.0, 139.6, 134.0, 129.3, 128.5, 126.2, 44.9, 39.7, 36.3, 34.8, 33.8, 33.1, 31.6, 26.6, 26.3, 26.3.

IR ($CDCl_3$, cm^{-1}) ν 3203, 3064, 3027, 2920, 2848, 2249, 1674, 1626, 1478, 1449, 1419, 904, 727, 648.

HRMS (ASAP) m/z $[C_{19}H_{26}NO]^+$ ($[M+H]^+$) calculated 284.2014, found 284.2015.

3-benzyl-5-methyl-5,6-dihydropyridin-2(1H)-one (**3ad**)



3ad

Yield: 16.3 mg, 81%, 10.0 : 1 *rr*. white solid.

$\mathbf{R_f}$ = 0.22 (EA/Hex 1:1).

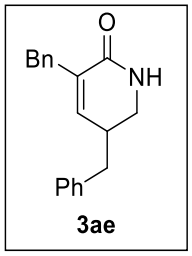
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 7.24 – 7.16 (m, 3H), 6.03 – 5.96 (m, 2H), 3.64 – 3.55 (m, 2H), 3.38 (dddd, J = 11.9, 6.0, 3.4, 0.9 Hz, 1H), 3.07 (ddd, J = 11.7, 9.1, 2.3 Hz, 1H), 2.63 – 2.53 (m, 1H), 1.05 (d, J = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 142.6, 139.5, 133.9, 129.4, 128.5, 126.2, 46.6, 36.1, 29.7, 17.5.

IR ($CDCl_3$, cm^{-1}) *v* 3241, 3061, 3027, 2962, 2926, 2871, 1674, 1626, 1476, 1277, 1076, 700.

HRMS (ASAP) m/z $[C_{13}H_{16}NO]^+$ ($[M+H]^+$) calculated 202.1232, found 202.1232.

3,5-dibenzyl-5,6-dihydropyridin-2(1H)-one (**3ae**)



3ae

Yield: 21.9 mg, 79%, 11.1 : 1 *rr*. off-white solid.

$\mathbf{R_f}$ = 0.34 (EA/Hex 1:1).

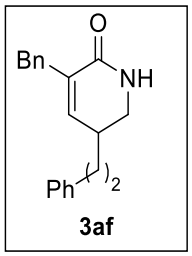
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 4H), 7.26 – 7.18 (m, 4H), 7.14 – 7.08 (m, 2H), 6.12 – 6.07 (m, 1H), 6.01 (s, 1H), 3.68 – 3.56 (m, 2H), 3.32 (ddd, *J* = 12.1, 5.3, 2.8 Hz, 1H), 3.12 (ddd, *J* = 12.2, 6.8, 3.0 Hz, 1H), 2.81 – 2.72 (m, 1H), 2.72 – 2.59 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 140.6, 139.4, 138.8, 134.7, 129.4, 129.0, 128.7, 128.5, 126.6, 126.3, 44.0, 38.2, 36.4, 36.2.

IR ($CDCl_3$, cm^{-1}) *v* 3215, 3060, 3025, 2918, 2855, 1672, 1625, 1493, 1476, 1452, 1285, 1076, 1028, 741, 699, 511.

HRMS (ASAP) m/z $[C_{19}H_{20}NO]^+$ ($[M+H]^+$) calculated 278.1545, found 278.1537.

3-benzyl-5-phenethyl-5,6-dihydropyridin-2(1H)-one (**3af**)



3af

Yield: 23.0 mg, 79%, 5.3 : 1 *rr*. off-white solid.

$\mathbf{R_f}$ = 0.41 (EA/Hex 1:1).

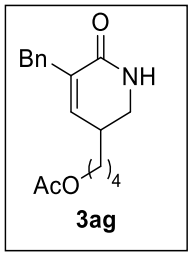
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 4H), 7.24 – 7.16 (m, 4H), 7.15 – 7.09 (m, 2H), 6.13 (s, 1H), 6.08 (d, *J* = 4.0 Hz, 1H), 3.61 (s, 2H), 3.44 (ddd, *J* = 12.2, 5.8, 3.0 Hz, 1H), 3.17 (ddd, *J* = 11.6, 7.9, 2.7 Hz, 1H), 2.66 – 2.55 (m, 2H), 2.47 – 2.37 (m, 1H), 1.90 – 1.65 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 141.3, 141.0, 139.4, 134.5, 129.4, 128.6, 128.5, 128.4, 126.3, 126.2, 44.5, 36.2, 33.9, 33.7, 33.2.

IR ($CDCl_3$, cm^{-1}) *v* 3213, 3060, 3025, 2922, 2856, 1672, 1625, 1493, 1477, 1452, 1267, 1074, 1030, 825, 746, 698.

HRMS (ASAP) m/z $[C_{20}H_{22}NO]^+$ ($[M+H]^+$) calculated 292.1701, found 292.1698.

4-(5-benzyl-6-oxo-1,2,3,6-tetrahydropyridin-3-yl)butyl acetate (**3ag**)



3ag

Yield: 24.4 mg, 81%, 8.5 : 1 *rr*. white solid.

R_f = 0.11 (EA/Hex 1:1).

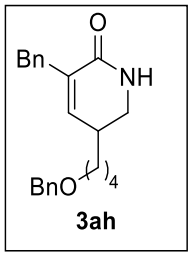
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 2H), 7.23 – 7.17 (m, 3H), 6.08 – 6.02 (m, 2H), 4.03 (t, *J* = 6.6 Hz, 2H), 3.63 – 3.57 (m, 2H), 3.41 (ddd, *J* = 12.1, 5.8, 3.1 Hz, 1H), 3.12 (ddd, *J* = 12.1, 8.2, 2.6 Hz, 1H), 2.44 – 2.35 (m, 1H), 2.03 (s, 3H), 1.64 – 1.56 (m, 2H), 1.50 – 1.28 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 166.8, 141.0, 139.4, 134.4, 129.3, 128.5, 126.3, 64.2, 44.6, 36.2, 34.5, 31.8, 28.7, 23.5, 21.1.

IR ($CDCl_3$, cm^{-1}) *v* 3216, 2062, 3027, 2929, 2858, 1734, 1673, 1626, 1476, 1453, 1365, 1236, 1034, 701.

HRMS (ASAP) m/z $[C_{18}H_{24}NO_3]^+$ ($[M+H]^+$) calculated 302.1756, found 302.1755.

3-benzyl-5-(4-(benzyloxy)butyl)-5,6-dihydropyridin-2(1H)-one (**3ah**)



3ah

Yield: 27.6 mg, 79%, 8.8 : 1 *rr*. yellow oil.

R_f = 0.21 (EA/Hex 1:1).

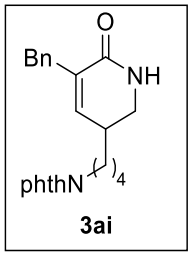
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 7H), 7.25 – 7.16 (m, 3H), 6.09 - 6.05 (m, 1H), 5.93 (s, 1H), 4.49 (s, 2H), 3.60 (s, 2H), 3.45 (t, *J* = 6.4 Hz, 2H), 3.39 (ddd, *J* = 12.0, 5.8, 3.1 Hz, 1H), 3.11 (ddd, *J* = 12.1, 8.3, 2.6 Hz, 1H), 2.46 – 2.35 (m, 1H), 1.67 – 1.54 (m, 2H), 1.52 – 1.33 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 141.3, 139.5, 138.6, 134.1, 129.3, 128.5, 128.5, 127.8, 127.7, 126.2, 73.1, 70.0, 44.6, 36.2, 34.6, 31.9, 29.8, 23.8.

IR ($CDCl_3$, cm^{-1}) *v* 3214, 3061, 3027, 2929, 2855, 1673, 1626, 1476, 1452, 1363, 1271, 1099, 735, 698.

HRMS (ASAP) m/z $[C_{23}H_{28}NO_2]^+$ ($[M+H]^+$) calculated 350.2120, found 350.2121.

2-(4-(5-benzyl-6-oxo-1,2,3,6-tetrahydropyridin-3-yl)butyl)isoindoline-1,3-dione (**3ai**)



3ai

Yield: 27.6 mg, 71%, 9.5 : 1 *rr*. yellow oil.

R_f = 0.10 (EA/Hex 1:1).

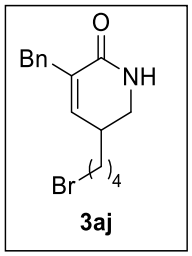
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.80 (m, 2H), 7.74 – 7.65 (m, 2H), 7.29 -7.23 (m, 2H), 7.21 – 7.14 (m, 3H), 6.07 – 6.02 (m, 2H), 3.66 (t, *J* = 7.2 Hz, 2H), 3.58 (s, 2H), 3.38 (ddd, *J* = 12.1, 5.9, 3.1 Hz, 1H), 3.10 (ddd, *J* = 11.6, 8.3, 2.6 Hz, 1H), 2.42 – 2.34 (m, 1H), 1.71 – 1.59 (m, 2H), 1.52 – 1.38 (m, 2H), 1.38 – 1.26 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.5, 166.8, 141.0, 139.4, 134.3, 134.1, 132.2, 129.3, 128.5, 126.2, 123.3, 44.5, 37.7, 36.2, 34.5, 31.6, 28.6, 24.3.

IR ($CDCl_3$, cm^{-1}) *v* 3218, 3061, 3027, 2931, 2858, 2243, 1770, 1705, 1672, 1624, 1395, 1365, 911, 718, 702.

HRMS (ASAP) m/z $[C_{24}H_{25}N_2O_3]^+$ ($[M+H]^+$) calculated 389.1865, found 389.1854.

3-benzyl-5-(4-bromobutyl)-5,6-dihydropyridin-2(1H)-one (**3aj**)



3aj

Yield: 24.5 mg, 76%, 8.0 : 1 *rr*. white solid.

R_f = 0.24 (EA/Hex 1:1).

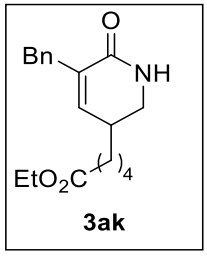
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.27 – 7.18 (m, 3H), 6.14 (s, 1H), 6.10 – 6.06 (m, 1H), 3.63 (s, 2H), 3.49 – 3.38 (m, 3H), 3.15 (ddd, *J* = 11.5, 8.2, 2.4 Hz, 1H), 2.49 – 2.36 (m, 1H), 1.91 – 1.79 (m, 2H), 1.53 – 1.39 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 140.9, 139.4, 134.5, 129.3, 128.5, 126.3, 44.6, 36.2, 34.4, 33.5, 32.6, 31.2, 25.5.

IR ($CDCl_3$, cm^{-1}) *v* 3216, 3061, 3026, 2927, 2856, 2247, 1672, 1625, 1476, 1453, 1270, 905, 727, 701, 647.

HRMS (ASAP) m/z $[C_{16}H_{21}BrNO]^+$ ($[M+H]^+$) calculated 322.0807, found 322.0798.

ethyl 5-(5-benzyl-6-oxo-1,2,3,6-tetrahydropyridin-3-yl)pentanoate (**3ak**)



3ak

Yield: 24.9 mg, 79%, 8.0 : 1 *rr*. white solid.

R_f = 0.28 (EA/Hex 1:1).

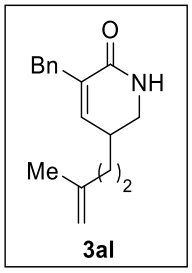
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.22 – 7.16 (m, 3H), 6.07 – 6.03 (m, 1H), 6.00 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.59 (s, 2H), 3.40 (ddd, *J* = 12.0, 5.9, 3.1 Hz, 1H), 3.11 (ddd, *J* = 11.6, 8.3, 2.6 Hz, 1H), 2.45 – 2.36 (m, 1H), 2.27 (t, *J* = 7.4 Hz, 2H), 1.66 – 1.54 (m, 2H), 1.51 – 1.36 (m, 2H), 1.36 – 1.27 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 166.9, 141.2, 139.5, 134.3, 129.3, 128.5, 126.2, 60.4, 44.6, 36.2, 34.4, 34.2, 31.8, 26.5, 24.9, 14.4.

IR ($CDCl_3$, cm^{-1}) *v* 3217, 3062, 3027, 2978, 2930, 2858, 1729, 1673, 1626, 1476, 1453, 1180, 1158, 727, 701.

HRMS (ASAP) m/z $[C_{19}H_{26}NO_3]^+$ ($[M+H]^+$) calculated 316.1913, found 316.1904.

3-benzyl-5-(3-methylbut-3-en-1-yl)-5,6-dihydropyridin-2(1H)-one (**3al**)



3al

Yield: 19.9 mg, 78%, 7.7 : 1 *rr*. yellow solid.

R_f = 0.41 (EA/Hex 1:1).

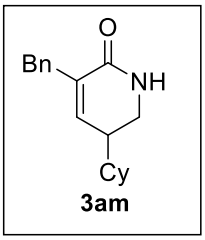
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.24 – 7.18 (m, 3H), 6.10 – 6.03 (m, 2H), 4.71 (s, 1H), 4.64 (s, 1H), 3.61 (s, 2H), 3.43 (ddd, *J* = 12.1, 5.8, 3.0 Hz, 1H), 3.14 (ddd, *J* = 12.1, 8.0, 2.6 Hz, 1H), 2.44 – 2.35 (m, 1H), 2.06 – 1.95 (m, 2H), 1.69 (s, 3H), 1.65 – 1.47 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 144.9, 141.2, 139.5, 134.3, 129.4, 128.5, 126.2, 110.8, 44.6, 36.2, 35.1, 34.0, 30.0, 22.4.

IR ($CDCl_3$, cm^{-1}) *v* 3217, 3066, 3026, 2966, 2924, 2856, 1672, 1625, 1476, 1451, 1371, 1265, 1074, 1029, 886, 825, 753, 699, 511.

HRMS (ASAP) m/z $[C_{17}H_{22}NO]^+$ ($[M+H]^+$) calculated 256.1701, found 256.1705.

3-benzyl-5-cyclohexyl-5,6-dihydropyridin-2(1H)-one (**3am**)



3am

Yield: 18.9 mg, 70%, 6.1 : 1 *rr*. off-white solid.

$\mathbf{R_f}$ = 0.44 (EA/Hex 1:1).

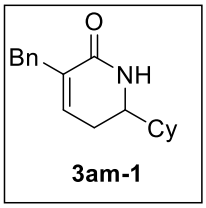
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.24 – 7.16 (m, 3H), 6.15 (d, *J* = 4.0 Hz, 1H), 5.78 (s, 1H), 3.62 (s, 2H), 3.35 (ddd, *J* = 12.0, 6.1, 3.0 Hz, 1H), 3.27 (ddd, *J* = 11.8, 8.2, 2.7 Hz, 1H), 2.24 – 2.16 (m, 1H), 1.77 – 1.61 (m, 4H), 1.48 – 1.38 (m, 1H), 1.25 – 1.04 (m, 4H), 1.03 – 0.91 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 140.4, 139.7, 134.3, 129.3, 128.5, 126.2, 42.3, 40.0, 39.9, 36.4, 30.6, 30.4, 26.4.

IR ($CDCl_3$, cm^{-1}) *v* 3217, 3061, 3026, 2922, 2850, 1673, 1625, 1478, 1449, 1273, 1075, 727, 699.

HRMS (ASAP) m/z $[C_{18}H_{24}NO]^+$ ($[M+H]^+$) calculated 270.1858, found 270.1863.

3-benzyl-6-cyclohexyl-5,6-dihydropyridin-2(1H)-one (**3am-1**)



3am-1

Yield: 19.4 mg, 72%, 1 : 7.3 *rr*. off-white solid.

$\mathbf{R_f}$ = 0.23 (EA/Hex 1:4).

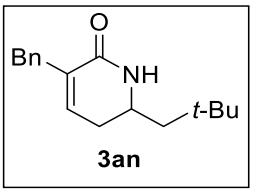
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.24 – 7.16 (m, 3H), 6.10 (ddt, *J* = 5.1, 3.3, 1.6 Hz, 1H), 5.59 (s, 1H), 3.63 (dd, *J* = 15.8, 2.0 Hz, 1H), 3.57 (dd, *J* = 15.8, 1.9 Hz, 1H), 3.37 – 3.28 (m, 1H), 2.29 – 2.14 (m, 2H), 1.81 – 1.64 (m, 5H), 1.43 – 1.34 (m, 1H), 1.30 – 1.06 (m, 3H), 1.04 – 0.92 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 139.6, 135.9, 134.8, 129.4, 128.5, 126.2, 55.9, 41.9, 36.1, 28.9, 28.8, 27.4, 26.4, 26.2, 26.1.

IR ($CDCl_3$, cm^{-1}) *v* 3206, 3062, 3027, 2923, 2852, 2244, 1672, 1629, 1450, 1428, 905, 727, 700, 648.

HRMS (ASAP) m/z $[C_{18}H_{24}NO]^+$ ($[M+H]^+$) calculated 270.1858, found 270.1861.

3-benzyl-6-neopentyl-5,6-dihydropyridin-2(1H)-one (**3an**)



3an

Yield: 14.2 mg, 55%, 1 : 3.3 *rr*. white solid.

R_f = 0.22 (EA/Hex 1:1).

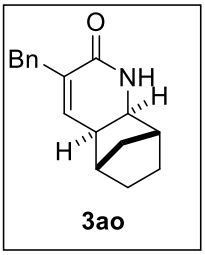
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 6.07 (ddt, *J* = 6.0, 3.0, 1.6 Hz, 1H) 5.45 (s, 1H), 3.69 – 3.54 (m, 3H), 2.28 – 2.18 (m, 1H), 2.19 – 2.10 (m, 1H), 1.47 (dd, *J* = 14.6, 6.7 Hz, 1H), 1.41 (dd, *J* = 14.5, 4.1 Hz, 1H), 0.94 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 139.5, 135.9, 134.9, 129.5, 128.5, 126.3, 50.1, 48.7, 36.1, 32.8, 30.6, 30.1.

IR ($CDCl_3$, cm^{-1}) *v* 3206, 3063, 3027, 2952, 2868, 1674, 1630, 1427, 1365, 904, 726, 649.

HRMS (ASAP) m/z $[C_{17}H_{24}NO]^+$ ($[M+H]^+$) calculated 258.1852, found 258.1852.

3-benzyl-4a,5,8,8a-tetrahydro-5,8-methanoquinolin-2(1H)-one (**3ao**)



3ao

Yield: 23.3 mg, 92%, off-white solid.

R_f = 0.38 (EA/Hex 1:1).

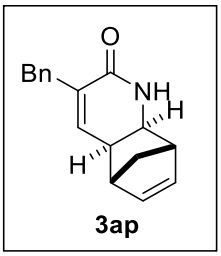
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.23 – 7.15 (m, 3H), 5.84 (d, *J* = 4.4 Hz, 1H), 5.72 (s, 1H), 3.63 – 3.50 (m, 3H), 2.48 – 2.41 (m, 1H), 2.09 (d, *J* = 3.9 Hz, 1H), 2.03 (d, *J* = 3.4 Hz, 1H), 1.71 (dt, *J* = 10.4, 2.1 Hz, 1H), 1.61 – 1.47 (m, 2H), 1.31 – 1.15 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7, 139.8, 137.6, 131.0, 129.3, 128.4, 126.1, 58.3, 46.5, 43.3, 42.7, 36.0, 32.6, 29.7, 25.8.

IR ($CDCl_3$, cm^{-1}) *ν* 3205, 3060, 3027, 2952, 2911, 2872, 2242, 1680, 1631, 1474, 1452, 1271, 904, 726, 700, 647.

HRMS (ASAP) m/z $[C_{17}H_{20}NO]^+$ ($[M+H]^+$) calculated 254.1545, found 254.1544.

3-benzyl-4a,5,6,7,8,8a-hexahydro-5,8-methanoquinolin-2(1H)-one (**3ap**)



3ap

Yield: 20.1 mg, 80%, off-white solid.

$\mathbf{R_f}$ = 0.44 (EA/Hex 1:1).

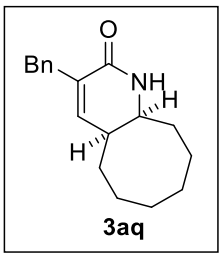
^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.34 – 7.25 (m, 3H), 7.21 (d, J = 7.8 Hz, 2H), 6.19 (dd, *J* = 5.8, 3.0 Hz, 1H), 6.08 - 5.99 (m, 2H), 5.98 – 5.94 (m, 1H), 3.66 – 3.54 (m, 2H), 3.49 (dt, *J* = 9.3, 1.9 Hz, 1H), 2.76 (s, 1H), 2.67 (s, 1H), 2.42-2.40 (m, 1H), 1.74 – 1.68 (m, 1H), 1.51 – 1.44 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) *δ* 165.1, 139.7, 139.0, 137.8, 134.7, 131.8, 129.3, 128.5, 126.2, 54.3, 52.5, 48.6, 42.9, 38.0, 36.3.

IR ($CDCl_3$, cm^{-1}) *ν* 3204, 3060, 3027, 2970, 2920, 2242, 1678, 1631, 1475, 1453, 1276, 905, 725, 699, 647, 508.

HRMS (ASAP) m/z $[C_{17}H_{18}NO]^+$ ($[M+H]^+$) calculated 252.1388, found 186.0923 (Retro Diels-Alder product).

3-benzyl-4a,5,6,7,8,9,10,10a-octahydrocycloocta[b]pyridin-2(1H)-one (**3aq**)



3aq

Yield: 20.2 mg, 75%, yellow solid.

R_f = 0.56 (EA/Hex 1:1).

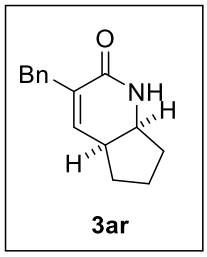
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 2H), 7.22 – 7.17 (m, 3H), 6.09 (dt, *J* = 6.3, 1.6 Hz, 1H), 5.54 – 5.37 (m, 1H), 3.70 – 3.51 (m, 3H), 2.50 – 2.42 (m, 1H), 1.86 – 1.71 (m, 2H), 1.74 – 1.55 (m, 5H), 1.56 – 1.34 (m, 4H), 1.34 – 1.24 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 142.6, 139.7, 132.3, 129.4, 128.5, 126.2, 54.1, 37.0, 35.8, 29.1, 28.4, 27.2, 25.4, 25.0, 23.6.

IR ($CDCl_3$, cm^{-1}) *v* 3205, 3061, 3027, 2919, 2852, 2242, 1672, 1628, 1451, 1428, 1293, 905, 726, 699, 647.

HRMS (ASAP) m/z $[C_{18}H_{24}NO]^+$ ($[M+H]^+$) calculated 270.1858, found 270.1857.

3-benzyl-1,4a,5,6,7,7a-hexahydro-2H-cyclopenta[b]pyridin-2-one (**3ar**)



3ar

Yield: 21.1 mg, 93%, off-white solid.

R_f = 0.34 (EA/Hex 1:1).

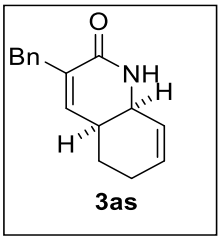
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.23 – 7.17 (m, 3H), 6.07 (dt, *J* = 5.1, 1.5 Hz, 1H), 5.59 (s, 1H), 3.98 – 3.92 (m, 1H), 3.63 (dt, *J* = 15.7, 1.6 Hz, 1H), 3.56 (dt, *J* = 15.8, 1.5 Hz, 1H), 2.66 – 2.57 (m, 1H), 2.00 – 1.86 (m, 2H), 1.85 – 1.73 (m, 1H), 1.72 – 1.62 (m, 1H), 1.65 – 1.51 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 139.7, 139.6, 132.2, 129.4, 128.5, 126.2, 55.5, 38.6, 36.1, 35.1, 32.2, 23.2.

IR ($CDCl_3$, cm^{-1}) *v* 3205, 3060, 3027, 2955, 2871, 1672, 1627, 1493, 1451, 1304, 1267, 907, 727, 699.

HRMS (ASAP) m/z $[C_{15}H_{18}NO]^+$ ($[M+H]^+$) calculated 228.1388, found 228.1391.

3-benzyl-4a,5,6,8a-tetrahydroquinolin-2(1H)-one (**3as**)



3as

Yield: 21.1 mg, 88%, >15 : 1 *rr*. white solid.

$\mathbf{R}_f$ = 0.48 (EA/Hex 1:1).

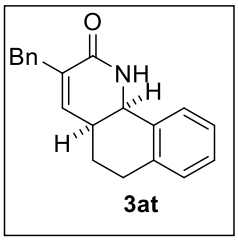
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.23 – 7.17 (m, 3H), 6.09 – 6.03 (m, 1H), 5.97 – 5.90 (m, 1H), 5.61 (ddd, *J* = 8.8, 4.4, 2.2 Hz, 1H), 5.49 (s, 1H), 4.07 – 4.02 (m, 1H), 3.65 (d, *J* = 15.9 Hz, 1H), 3.57 (d, *J* = 15.9 Hz, 1H), 2.46 – 2.38 (m, 1H), 2.13 – 2.04 (m, 1H), 2.04 – 1.94 (m, 1H), 1.68 – 1.55 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8, 140.1, 139.6, 134.1, 131.4, 129.4, 128.5, 126.2, 125.1, 48.3, 36.1, 34.1, 24.3, 22.8.

IR ($CDCl_3$, cm^{-1}) *v* 3208, 3060, 3024, 2922, 1673, 1627, 1452, 1429, 1286, 1263, 736, 699.

HRMS (ASAP) m/z $[C_{16}H_{18}NO]^+$ ($[M+H]^+$) calculated 240.1388, found 240.1388.

3-benzyl-4a,5,6,10b-tetrahydrobenzo[h]quinolin-2(1H)-one (**3at**)



3at

Yield: 18.2 mg, 63%, >13.1 : 1 *rr*. white solid.

$\mathbf{R}_f$ = 0.58 (EA/Hex 1:1).

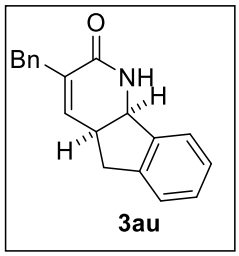
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.29 – 7.18 (m, 6H), 7.21 – 7.13 (m, 1H), 6.24 (dt, *J* = 6.0, 1.5 Hz, 1H), 5.42 (s, 1H), 4.69 (d, *J* = 5.0 Hz, 1H), 3.71 (d, *J* = 15.7 Hz, 1H), 3.59 (d, *J* = 15.8 Hz, 1H), 2.88 (ddd, *J* = 17.0, 5.2, 2.9 Hz, 1H), 2.76 (ddd, *J* = 17.1, 11.8, 5.6 Hz, 1H), 2.54 – 2.46 (m, 1H), 1.95 – 1.84 (m, 1H), 1.81 – 1.73 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 140.0, 139.4, 136.7, 134.4, 134.4, 129.6, 129.4, 128.8, 128.5, 128.4, 127.0, 126.3, 51.7, 36.1, 35.0, 28.8, 22.6.

IR ($CDCl_3$, cm^{-1}) *v* 3401, 3205, 3060, 3025, 2924, 2244, 1671, 1629, 1493, 1452, 1427, 1266, 906, 726, 700.

HRMS (ASAP) m/z $[C_{20}H_{20}NO]^+$ ($[M+H]^+$) calculated 290.1545, found 290.1541.

3-benzyl-1,4a,5,9b-tetrahydro-2H-indeno[1,2-b]pyridin-2-one (**3au**)



3au

Yield: 20.4 mg, 74%, 14.7 : 1 *rr*. yellow solid.

R_f = 0.46 (EA/Hex 1:1).

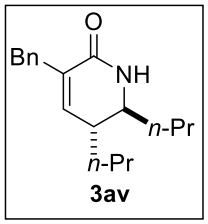
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.16 (m, 7H), 7.12 – 7.06 (m, 2H), 6.49 (s, 1H), 6.06 – 6.02 (m, 1H), 4.94 – 4.87 (m, 1H), 3.64 (d, *J* = 15.9 Hz, 1H), 3.54 (d, *J* = 15.9 Hz, 1H), 3.37 – 3.29 (m, 1H), 3.22 (dd, *J* = 15.6, 7.9 Hz, 1H), 2.90 (dd, *J* = 15.5, 5.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.0, 142.7, 141.3, 139.4, 139.1, 133.7, 129.2, 128.4, 128.4, 127.3, 126.16, 124.9, 123.9, 58.3, 39.0, 38.2, 36.1.

IR ($CDCl_3$, cm^{-1}) *v* 3203, 3061, 3026, 2906, 2850, 2243, 1674, 1628, 1477, 1453, 907, 729, 698.

HRMS (ASAP) m/z $[C_{19}H_{18}NO]^+$ ($[M+H]^+$) calculated 276.1388, found 276.1388.

3-benzyl-5,6-dipropyl-5,6-dihydropyridin-2(1H)-one (**3av**)



3av

Yield: 15.2 mg. 56%, yellow solid.

R_f = 0.21 (EA/Hex 1:4).

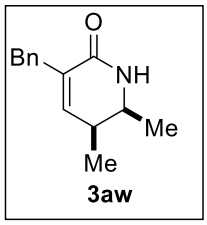
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 2H), 7.26 – 7.14 (m, 3H), 6.0f6 – 6.00 (m, 1H), 5.75 (s, 1H), 3.64 – 3.55 (m, 2H), 3.28 – 3.19 (m, 1H), 2.20 – 2.11 (m, 1H), 1.60 – 1.47 (m, 1H), 1.49 – 1.21 (m, 7H), 0.90 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8, 140.1, 139.6, 133.3, 129.3, 128.5, 126.2, 54.7, 38.8, 37.2, 36.1, 34.9, 20.0, 19.0, 14.3, 14.0.

IR ($CDCl_3$, cm^{-1}) *v* 3205, 3062, 3027, 2956, 2928, 2870, 1674, 1629, 1454, 1430, 699.

HRMS (ASAP) m/z $[C_{18}H_{26}NO]^+$ ($[M+H]^+$) calculated 272.2014, found 272.2011.

3-benzyl-5,6-dimethyl-5,6-dihydropyridin-2(1H)-one (**3aw**)



3aw

Yield: 11.0 mg. 51%, yellow oil.

R_f = 0.37 (EA/Hex 1:1).

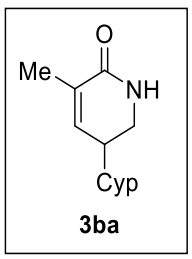
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 2H), 7.23 – 7.16 (m, 3H), 6.11 (dt, *J* = 5.6, 1.6 Hz, 1H), 5.43 (s, 1H), 3.76 – 3.70 (m, 1H), 3.67 – 3.60 (m, 1H), 3.5 – 3.52 (m, 1H), 2.36 – 2.29 (m, 1H), 1.13 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 142.4, 139.6, 133.4, 129.4, 128.5, 126.2, 49.5, 36.0, 33.8, 17.0, 11.9.

IR ($CDCl_3$, cm^{-1}) *v* 3206, 3061, 3027, 2969, 2921, 1671, 1626, 1453, 1424, 903, 725, 649.

HRMS (ASAP) m/z $[C_{14}H_{18}NO]^+$ ($[M+H]^+$) calculated 216.1388, found 216.1386.

5-cyclopentyl-3-methyl-5,6-dihydropyridin-2(1H)-one (**3ba**)



3ba

Yield: 11.1 mg, 62%, >15 : 1 *rr*. white solid.

R_f = 0.21 (EA/Hex 1:1).

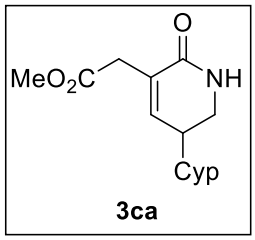
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (s, 1H), 6.08 (s, 1H), 3.40 (ddd, *J* = 12.0, 5.9, 3.3 Hz, 1H), 3.18 (ddd, *J* = 11.8, 9.2, 2.3 Hz, 1H), 2.27 – 2.17 (m, 1H), 1.89 – 1.79 (m, 5H), 1.82 – 1.72 (m, 1H), 1.69 – 1.59 (m, 2H), 1.58 – 1.48 (m, 2H), 1.29 – 1.08 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 140.1, 130.3, 44.8, 42.1, 40.2, 31.0, 30.4, 25.4, 25.3, 17.0.

IR ($CDCl_3$, cm^{-1}) *v* 3201, 3071, 2948, 2867, 1675, 1631, 1483, 1273, 856, 810.

HRMS (ASAP) m/z $[C_{11}H_{18}NO]^+$ ($[M+H]^+$) calculated 180.1388, found 180.1387.

methyl 2-(5-cyclopentyl-2-oxo-1,2,5,6-tetrahydropyridin-3-yl)acetate (**3ca**)



3ca

Yield: 17.3 mg, 69%, 9.3 : 1 *rr*. yellow oil.

R_f = 0.16 (EA/Hex 1:1).

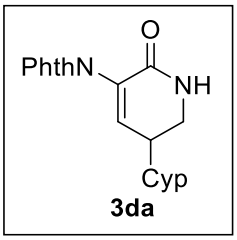
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.48 (d, *J* = 3.6 Hz, 1H), 5.91 (s, 1H), 3.68 (s, 3H), 3.45 (ddd, *J* = 12.1, 6.0, 3.3 Hz, 1H), 3.36 – 3.20 (m, 3H), 2.36 – 2.27 (m, 1H), 1.94 – 1.73 (m, 3H), 1.71 – 1.59 (m, 2H), 1.59 – 1.47 (m, 2H), 1.29 – 1.10 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 166.2, 143.1, 128.0, 52.1, 44.5, 42.0, 40.3, 35.9, 31.0, 30.4, 25.3, 25.2.

IR ($CDCl_3$, cm^{-1}) *v* 3222, 2949, 2866, 1737, 1677, 1631, 1478, 1339, 1263, 1208, 1159, 1018, 904, 797, 725, 648.

HRMS (ASAP) m/z $[C_{13}H_{20}NO_3]^+$ ($[M+H]^+$) calculated 238.1443, found 238.1442.

2-(5-cyclopentyl-2-oxo-1,2,5,6-tetrahydropyridin-3-yl)isoindoline-1,3-dione (**3da**)



3da

Yield: 14.9 mg, 48%, 4.4 : 1 *rr*. yellow solid.

$\mathbf{R}_f$ = 0.17 (EA/Hex 1:1).

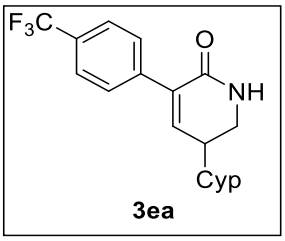
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 – 7.87 (m, 2H), 7.77 – 7.72 (m, 2H), 6.76 (d, *J* = 3.7 Hz, 1H), 6.07 (s, 1H), 3.59 (ddd, *J* = 12.4, 5.8, 3.3 Hz, 1H), 3.41 (ddd, *J* = 12.3, 8.6, 2.5 Hz, 1H), 2.65 – 2.58 (m, 1H), 2.09 – 1.91 (m, 2H), 1.90 – 1.80 (m, 1H), 1.75 – 1.61 (m, 2H), 1.64 – 1.53 (m, 2H), 1.36 – 1.17 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 161.6, 145.3, 134.4, 132.2, 124.8, 123.9, 44.1, 42.0, 40.6, 31.2, 30.4, 25.4, 25.2.

IR ($CDCl_3$, cm^{-1}) *v* 3226, 3085, 2950, 2867, 1777, 1720, 1684, 1641, 1470, 1378, 1113, 1086, 907, 717, 531.

HRMS (ASAP) m/z $[C_{18}H_{19}N_2O_3]^+$ ($[M+H]^+$) calculated 311.1396, found 311.1386.

5-cyclopentyl-3-(4-(trifluoromethyl)phenyl)-5,6-dihydropyridin-2(1H)-one (**3ea**)



3ea

Yield: 19.0 mg, 61%, 12.6 : 1 *rr*. yellow solid.

$\mathbf{R}_f$ = 0.42 (EA/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 – 7.53 (m, 4H), 6.76 (d, *J* = 3.6 Hz, 1H), 6.54 (s, 1H), 3.52 (ddd, *J* = 12.2, 5.9, 3.5 Hz, 1H), 3.31 (ddd, *J* = 12.0, 9.0, 2.5 Hz, 1H), 2.49 – 2.41 (m, 1H), 2.02 – 1.87 (m, 2H), 1.87 – 1.80 (m, 1H), 1.75 – 1.63 (m, 2H), 1.66 – 1.53 (m, 2H), 1.37 – 1.16 (m, 2H).

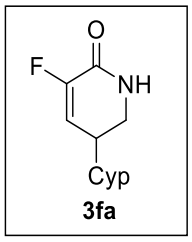
^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8, 143.9, 140.3, 134.1, 129.8 (q, *J* = 32.4 Hz), 129.1, 125.07 (q, *J* = 3.8 Hz), 124.34 (q, *J* = 271.9 Hz), 44.4, 42.0, 40.6, 31.1, 30.5, 25.4, 25.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6.

IR ($CDCl_3$, cm^{-1}) *v* 3206, 3102, 3058, 2960, 2875, 1670, 1613, 1475, 1320, 1164, 1120, 1067, 834.

HRMS (ASAP) m/z $[C_{17}H_{19}F_3NO]^+$ ($[M+H]^+$) calculated 310.1419, found 310.1419.

5-cyclopentyl-3-fluoro-5,6-dihydropyridin-2(1H)-one (**3fa**)



3fa

Yield: 13.4 mg, 73%, >15 : 1 *rr*. white solid.

$\mathbf{R_f}$ = 0.26 (EA/Hex 1:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (s, 1H), 6.07 (dd, *J* = 12.2, 4.0 Hz, 1H), 3.46 (ddd, *J* = 12.4, 5.8, 3.0 Hz, 1H), 3.25 (ddd, *J* = 12.5, 8.5, 2.5 Hz, 1H), 2.45 – 2.36 (m, 1H), 1.95 – 1.76 (m, 3H), 1.70 – 1.61 (m, 2H), 1.60 – 1.49 (m, 2H), 1.23 – 1.06 (m, 2H).

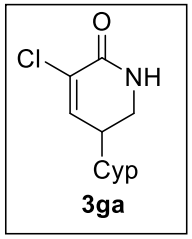
^{13}C NMR (126 MHz, $CDCl_3$) δ 161.4 (d, *J* = 31.6 Hz), 149.4 (d, *J* = 255.6 Hz), 119.0 (d, *J* = 10.9 Hz), 44.5, 42.3 (d, *J* = 2.1 Hz), 39.0 (d, *J* = 4.5 Hz), 31.0, 30.4, 25.32, 25.27.

^{19}F NMR (471 MHz, $CDCl_3$) δ -129.06 (m).

IR ($CDCl_3$, cm^{-1}) *v* 3241, 3097, 2948, 2867, 1693, 1650, 1478, 1233, 1198, 905, 815, 772, 722.

HRMS (ASAP) m/z $[C_{10}H_{15}FNO]^+$ ($[M+H]^+$) calculated 184.1138, found 184.1131.

3-chloro-5-cyclopentyl-5,6-dihydropyridin-2(1H)-one (**3ga**)



3ga

Yield: 15.2 mg, 76%, >15 : 1 *rr*. white solid.

$\mathbf{R_f}$ = 0.34 (EA/Hex 1:1).

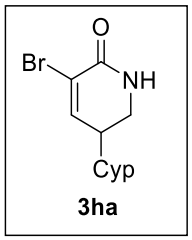
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.74 (d, J = 3.9 Hz, 1H), 3.48 (ddd, J = 12.4, 5.9, 3.3 Hz, 1H), 3.27 (ddd, J = 12.0, 9.0, 2.4 Hz, 1H), 2.43 – 2.34 (m, 1H), 1.95 – 1.74 (m, 3H), 1.71 – 1.61 (m, 2H), 1.60 – 1.50 (m, 2H), 1.27 – 1.09 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.3, 141.4, 126.9, 44.4, 41.8, 41.6, 31.0, 30.4, 25.3, 25.2.

IR ($CDCl_3$, cm^{-1}) ν 3202, 3104, 2938, 2867, 1671, 1609, 1480, 1411, 1353, 1260, 1102, 1046, 858, 801, 547.

HRMS (ASAP) m/z $[C_{10}H_{15}ClNO]^+$ ($[M+H]^+$) calculated 200.0842, found 200.0828.

3-bromo-5-cyclopentyl-5,6-dihydropyridin-2(1H)-one (**3ha**)



3ha

Yield: 20.3 mg, 83%, >15 : 1 *rr*. yellow solid.

R_f = 0.34 (EA/Hex 1:1).

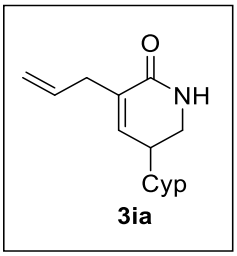
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (d, J = 3.8 Hz, 1H), 6.91 (s, 1H), 3.49 (ddd, J = 12.4, 5.9, 3.4 Hz, 1H), 3.28 (ddd, J = 12.0, 9.1, 2.4 Hz, 1H), 2.39 – 2.30 (m, 1H), 1.95 – 1.83 (m, 2H), 1.84 – 1.74 (m, 1H), 1.70 – 1.61 (m, 2H) 1.60 – 1.49 (m, 2H), 1.31 – 1.09 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.0, 146.2, 117.9, 44.6, 42.8, 41.7, 31.0, 30.4, 25.3, 25.2.

IR ($CDCl_3$, cm^{-1}) ν 3199, 3098, 2937, 2865, 1667, 1604, 1477, 1406, 1351, 1259, 904, 728, 537.

HRMS (ASAP) m/z $[C_{10}H_{15}BrNO]^+$ ($[M+H]^+$) calculated 244.0337, found 244.0330.

3-allyl-5-cyclopentyl-5,6-dihydropyridin-2(1H)-one (**3ia**)



3ia

Yield: 14.3 mg, 70%, 6.1 : 1 *rr*. yellow solid.

R_f = 0.31 (EA/Hex 1:1).

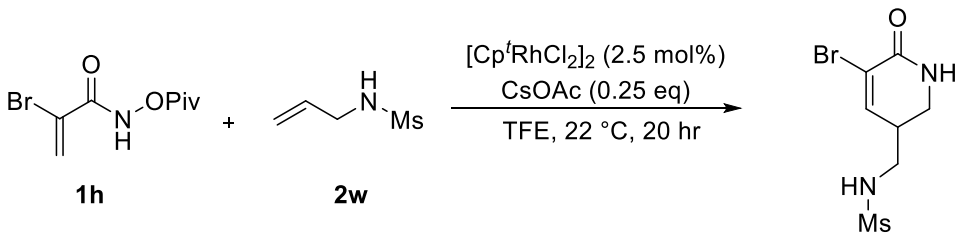
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.34 – 6.29 (m, 1H), 5.95 (s, 1H), 5.86 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.11 – 5.03 (m, 2H), 3.40 (ddd, *J* = 12.1, 5.9, 3.3 Hz, 1H), 3.19 (ddd, *J* = 11.8, 8.9, 2.4 Hz, 1H), 3.09 – 2.96 (m, 2H), 2.31 – 2.20 (m, 1H), 1.90 – 1.72 (m, 3H), 1.70 – 1.59 (m, 2H), 1.59 – 1.47 (m, 2H), 1.28 – 1.08 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 140.2, 136.0, 132.8, 116.5, 44.5, 42.1, 40.2, 34.4, 31.0, 30.4, 25.3, 25.2.

IR ($CDCl_3$, cm^{-1}) *v* 3216, 3073, 2948, 2866, 1674, 1626, 1477, 1267, 905, 724, 648.

HRMS (ASAP) m/z $[C_{13}H_{20}NO]^+$ ($[M+H]^+$) calculated 206.1545, found 206.1545.

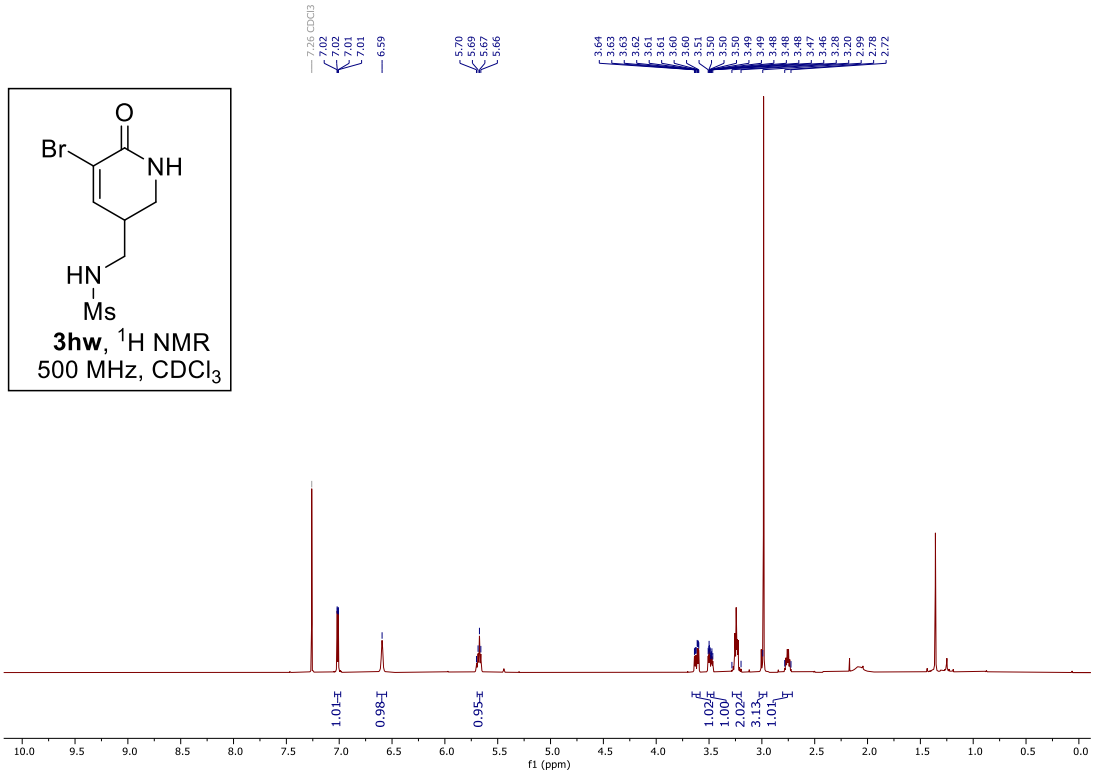
6. Product Derivatization

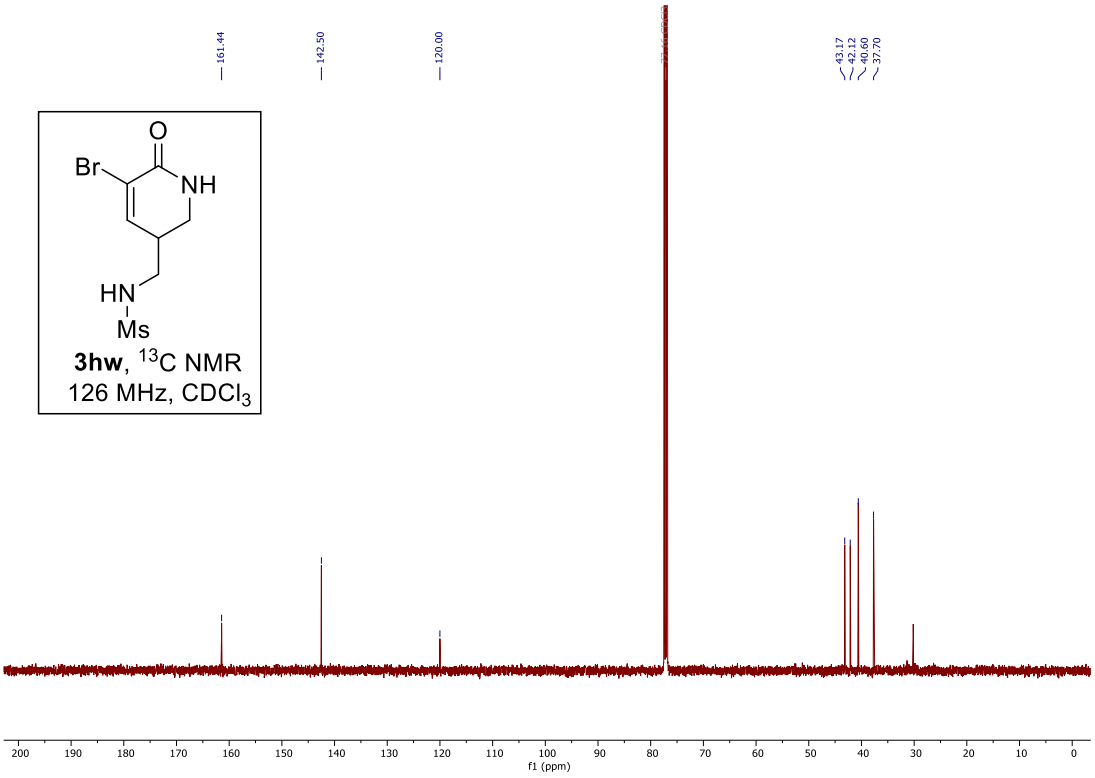


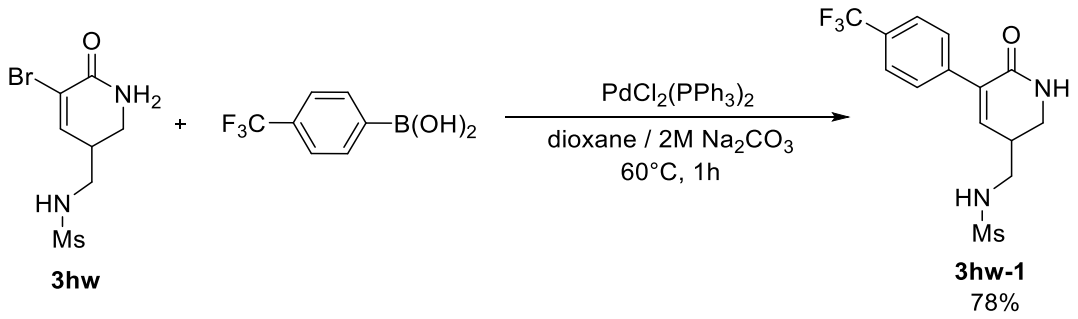
3hw, 66%
4.6 : 1 *rr*

3hw was synthesized following general procedure using **1h** and **2w**[9]. **Yield**: 18.7 mg, 66%, yellow oil. **R_f** = 0.15 (5% MeOH in DCM). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.04 – 6.98 (m, 1H), 6.59 (s, 1H), 5.67 (t, *J* = 6.6 Hz, 1H), 3.62 (ddd, *J* = 12.9, 5.6, 2.1 Hz, 1H), 3.52 – 3.45 (m, 1H), 3.28 – 3.21 (m, 2H), 2.98 (s, 3H), 2.80 – 2.71 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.4, 142.5, 120.0, 43.2, 42.1, 40.6, 37.7. **IR** ($CDCl_3$,

cm^{-1}) *v* 3270, 2928, 2873, 1667, 1609, 1473, 1446, 1313, 1148, 1102, 980, 761, 521. **HRMS** (ASAP) m/z $[C_7H_{12}BrN_2O_3S]^+$ ($[M+H]^+$) calculated 282.9752, found 282.9751

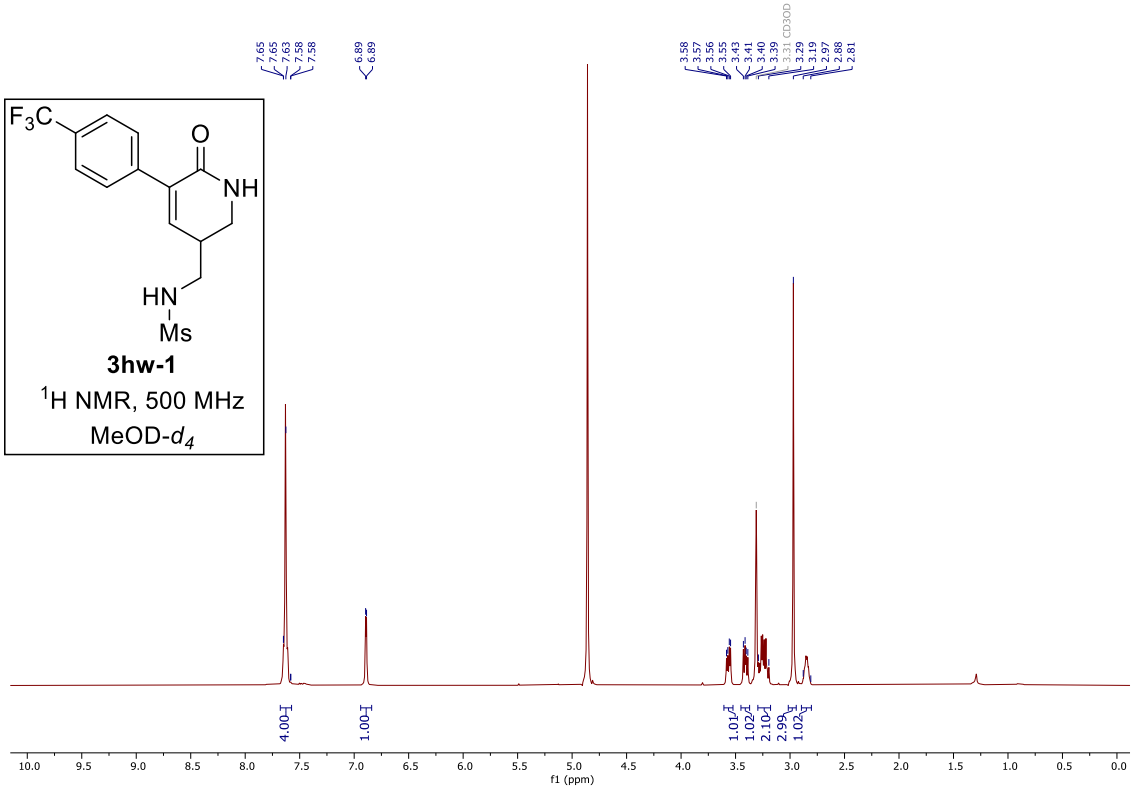


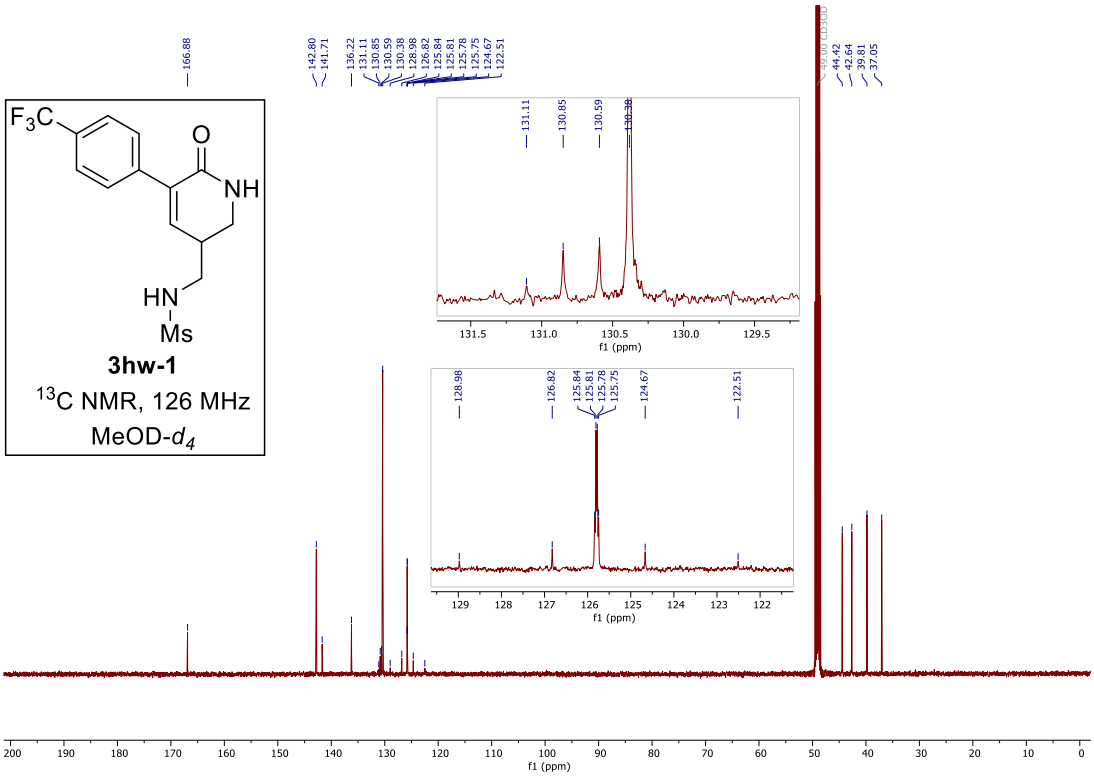




3hw (0.18 mmol, 1 equiv.), $PdCl_2(PPh_3)_2$ (0.018 mmol, 10 mol%), and (4-(trifluoromethyl)phenyl)boronic acid (0.54 mmol, 3 equiv) were measured in a 10 mL round-bottom flask. After the addition of 1.5 mL of dioxane, the mixture was purged with argon for 10 min. Separately, 1.5 mL of 2.0 M Na_2CO_3 solution in water was purged with argon 10 min and added to the flask. Then, the reaction mixture was heated to 60 °C and stirred for 1 hour. After completion, organic layer was collected and aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solid was filtered and the filtrate was concentrated by rotary evaporator. Purification was performed by flash chromatography using 5% MeOH in DCM as the eluent. **Yield**: 47.7 mg, 78%, white solid. $\mathbf{R_f}$ = 0.23 (5% MeOH in DCM). **^{1}H NMR** (500 MHz, MeOD-d_4) δ 7.67 – 7.59 (m, 4H), 6.89 (d, J =

4.3 Hz, 1H), 3.56 (dd, J = 12.7, 5.8 Hz, 1H), 3.41 (dd, J = 12.7, 7.7 Hz, 1H), 3.30 – 3.18 (m, 2H), 2.97 (s, 3H), 2.88 – 2.81 (m, 1H). **^{13}C NMR** (126 MHz, MeOD-d_4) δ 166.9, 142.8, 141.7, 136.2, 130.7 (q, J = 32.8 Hz), 130.4, 125.79 (q, J = 3.9 Hz), 125.74 (q, J = 271.1 Hz), 44.42, 42.64, 39.81, 37.05. **^{19}F NMR** (471 MHz, MeOD-d_4) δ -63.2. **IR** (MeOD-d_4, cm^{-1}) v 3216, 3073, 2948, 2866, 1674, 1626, 1477, 1267, 905, 724, 648. **HRMS** (ASAP) m/z $[C_{14}H_{16}F_3N_2O_3S]^+$ ($[M+H]^+$) calculated 349.0834, found 349.0839.




F3C
O
NH
HN
Ms
3hw-1
13C NMR, 126 MHz
MeOD-d4
166.88
142.80
141.71
136.22
131.11
130.85
130.59
130.38
128.98
126.82
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49.00
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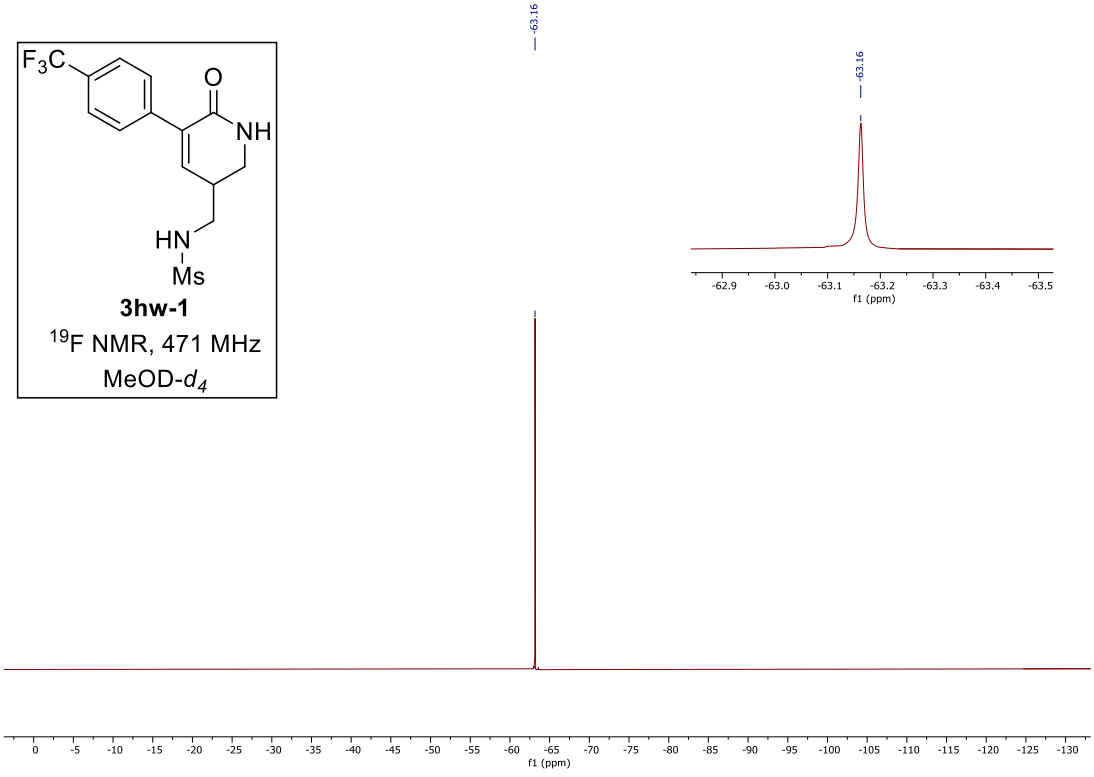
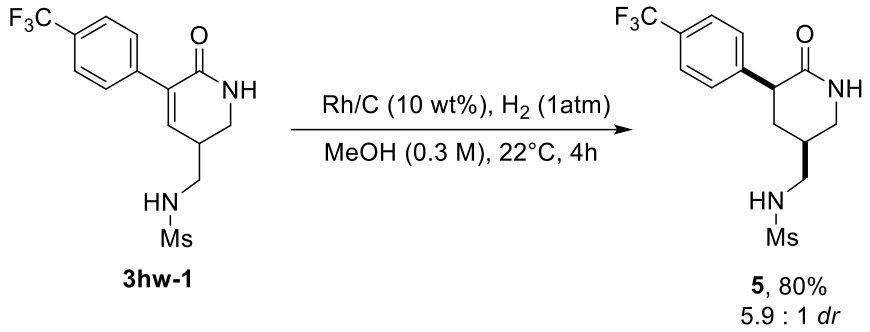
42.64
39.81
37.05
f1 (ppm)

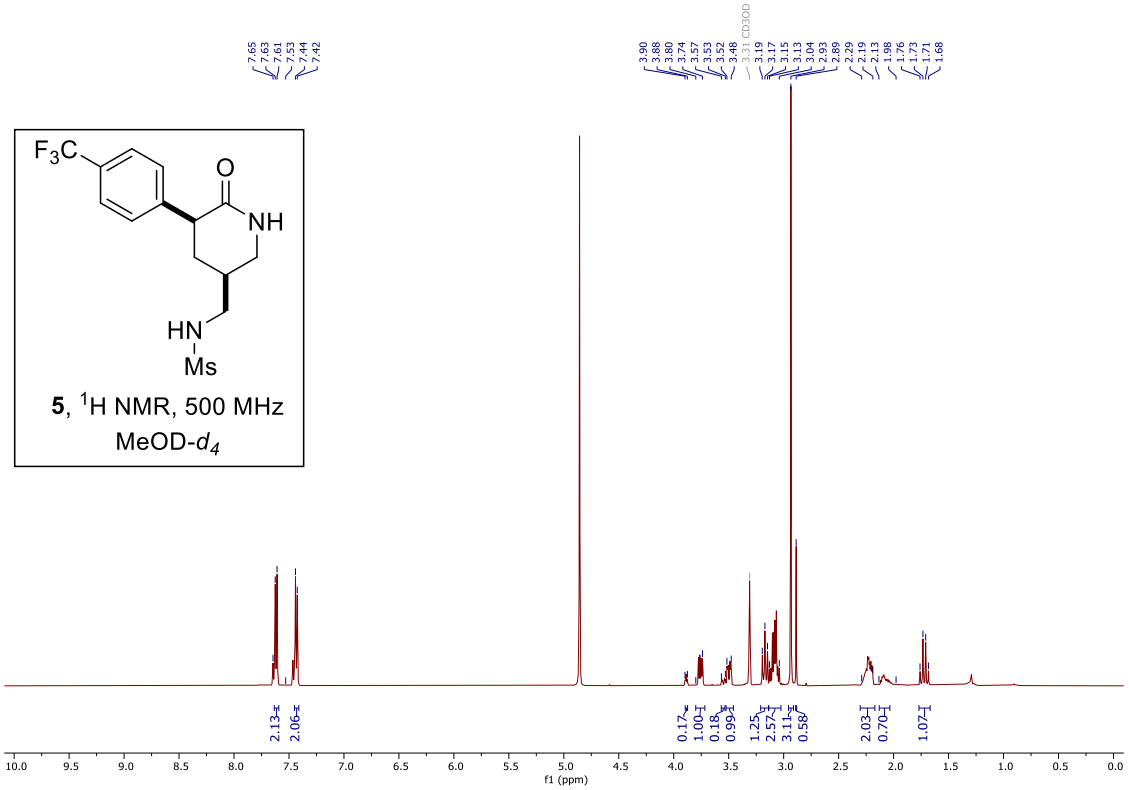

F3C
O
NH
HN
Ms
3hw-1
19F NMR, 471 MHz
MeOD-d4
-63.16
f1 (ppm)



3hw-1

5, 80%
5.9 : 1 *dr*

To a 10 mL round-bottom flack, **3hw-1** (0.244 mmol, 1 equiv.) was measure and dissolved in 0.8 mL of MeOH (0.3 M). The flask was charged with argon and Rh/C (10 wt%) was quickly added. Then the flask was evacuated and refilled with H_2 (1 atm) and stirred at 22 °C for 4 h. After completion, the reaction mixture was filtered through a Celite plug and washed with EtOAc. The solvent was removed in vacuo and purified by flash chromatography using 5-10% MeOH in DCM as the eluent to afford product **5**. **Yield**: 68.3 mg, 80%, white solid. *dr* = 5.9 : 1 $\mathbf{R_f}$ = 0.11 (5% MeOH in DCM). **Major isomer: ^{1}H NMR** (500 MHz, MeOD-d_4) δ 7.62 (m, 2H), 7.44 (m, 2H), 3.76 (dd, J = 12.3, 6.1 Hz, 1H), 3.52 – 3.46 (m, 1H), 3.21 – 3.14 (m, 1H), 3.13 – 3.03 (m, 2H), 2.93 (s, 3H), 2.30 – 2.17 (m, 2H), 1.72 (q, J = 12.9 Hz, 1H). **Major isomer: ^{13}C NMR** (126 MHz, MeOD-d_4) δ 174.66, 147.08, 130.47, 130.0 (q, J = 32.2 Hz), 126.35 (q, J = 3.8 Hz), 125.77 (q, J = 271.0 Hz), 49.24, 46.65, 46.54, 39.68, 35.99, 35.82. **^{19}F NMR** (471 MHz, MeOD-d_4) δ -63.04, -63.07. **IR** (MeOD-d_4, cm^{-1}) ν 3289, 2931, 2460, 2242, 2070, 1632, 1324, 1158, 1118, 1067, 972, 841. **HRMS** (ASAP) m/z $[C_{14}H_{16}N_2O_3SF_3]^+$ ($[M\text{-}H]^-$) calculated 349.0834, found 349.0815.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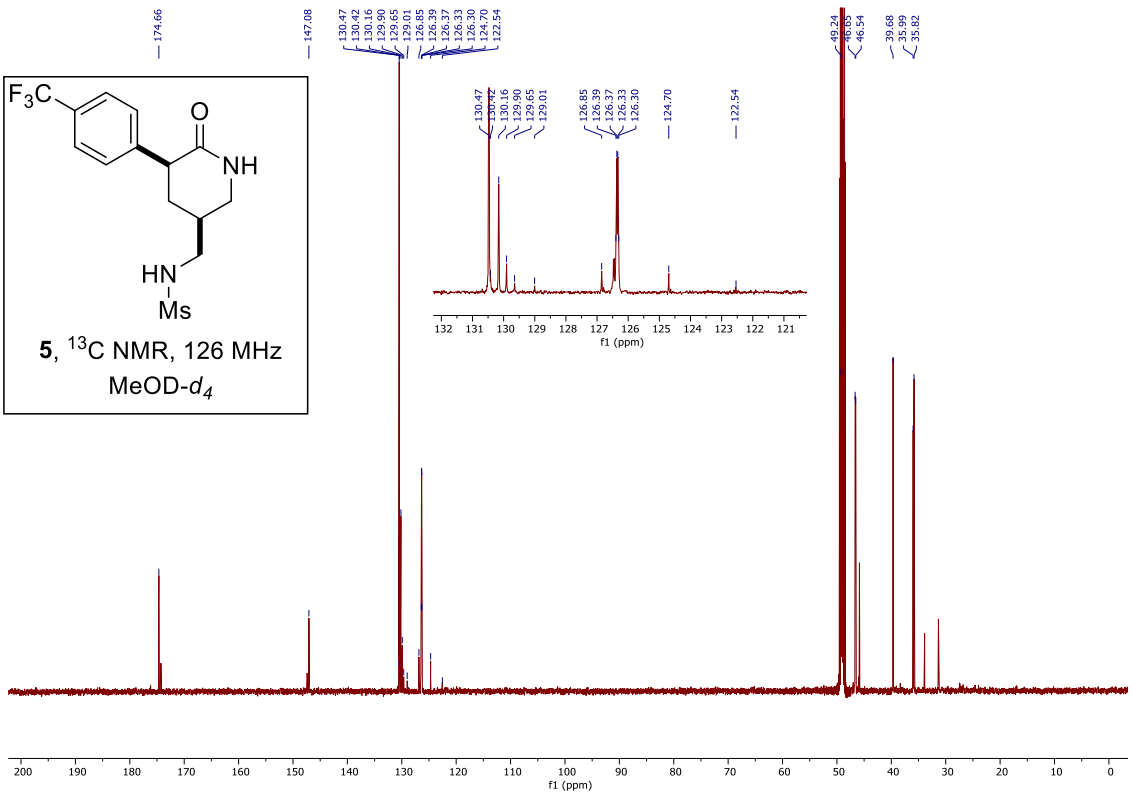
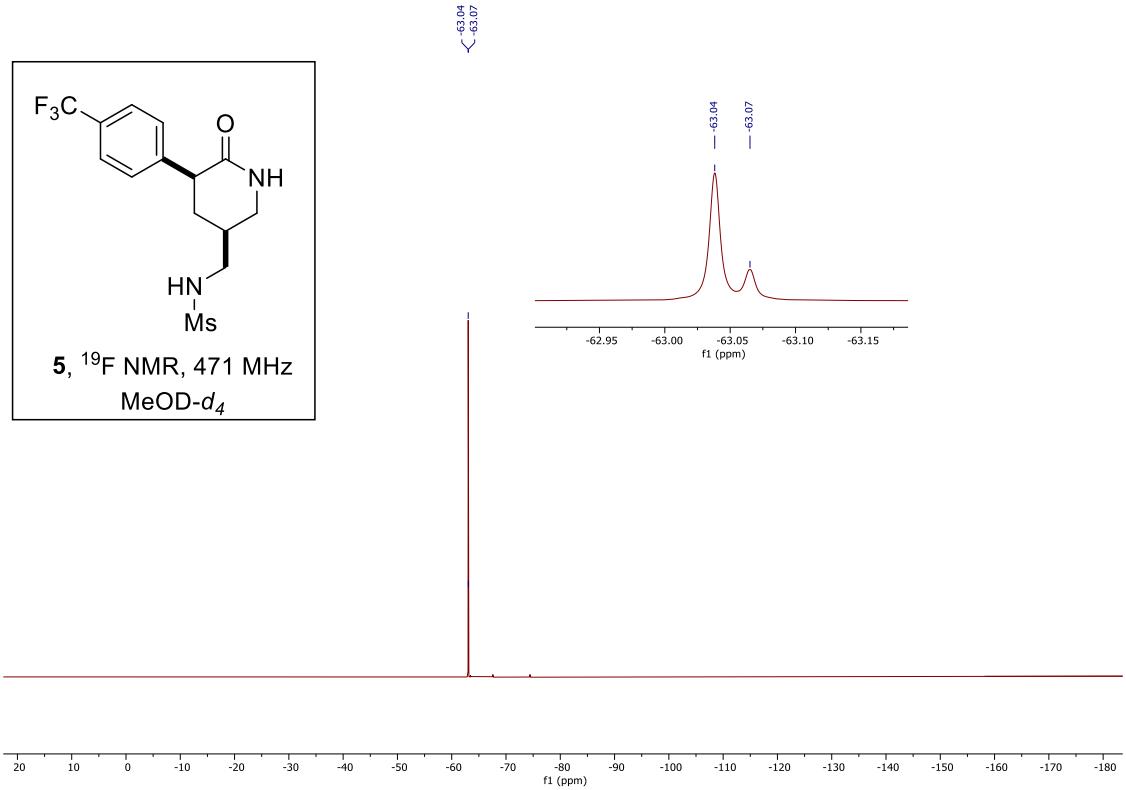
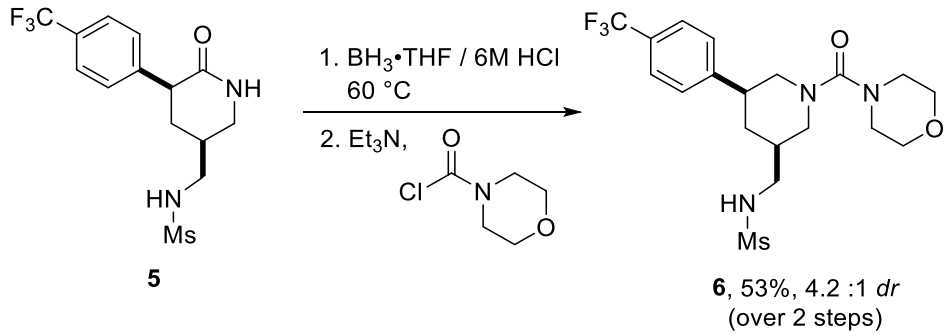
O
NH
HN
Ms
5, 1H NMR, 500 MHz
MeOD-d4
f1 (ppm)

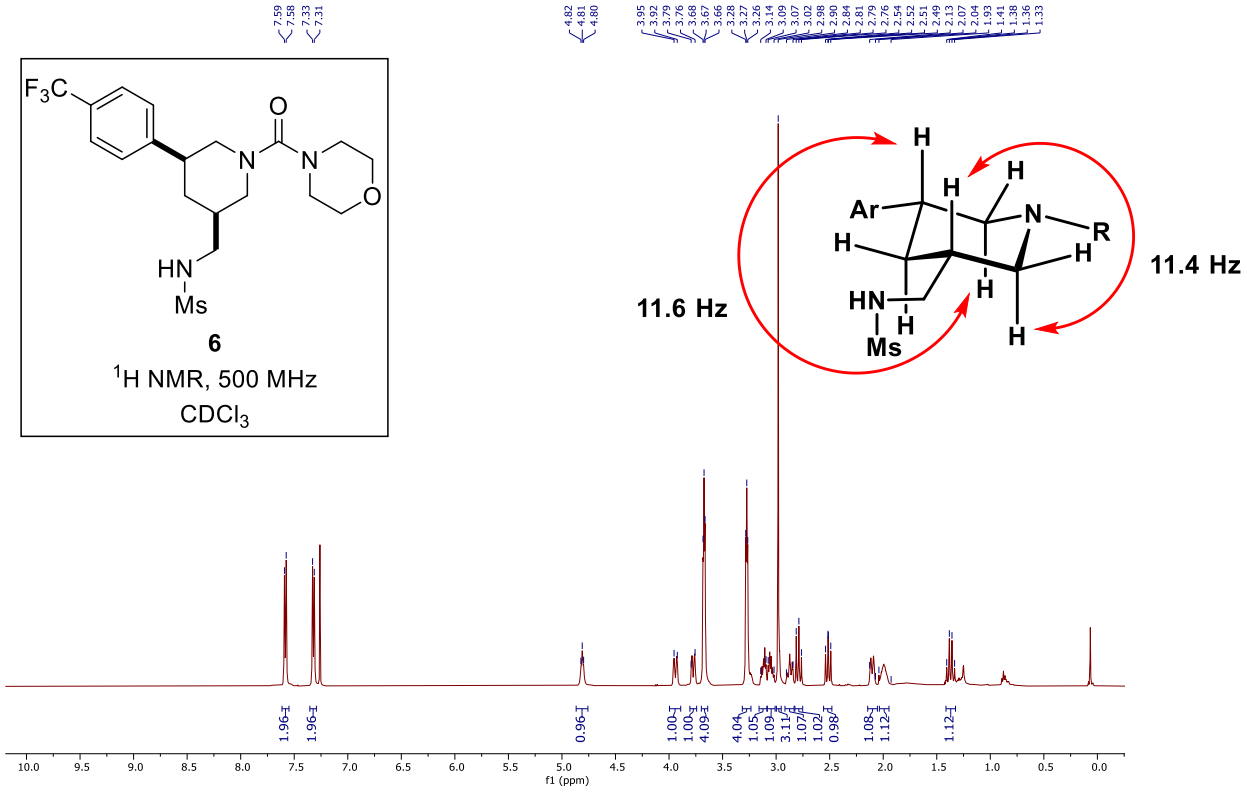

F3C
O
NH
HN
Ms
5, 13C NMR, 126 MHz
MeOD-d4
f1 (ppm)

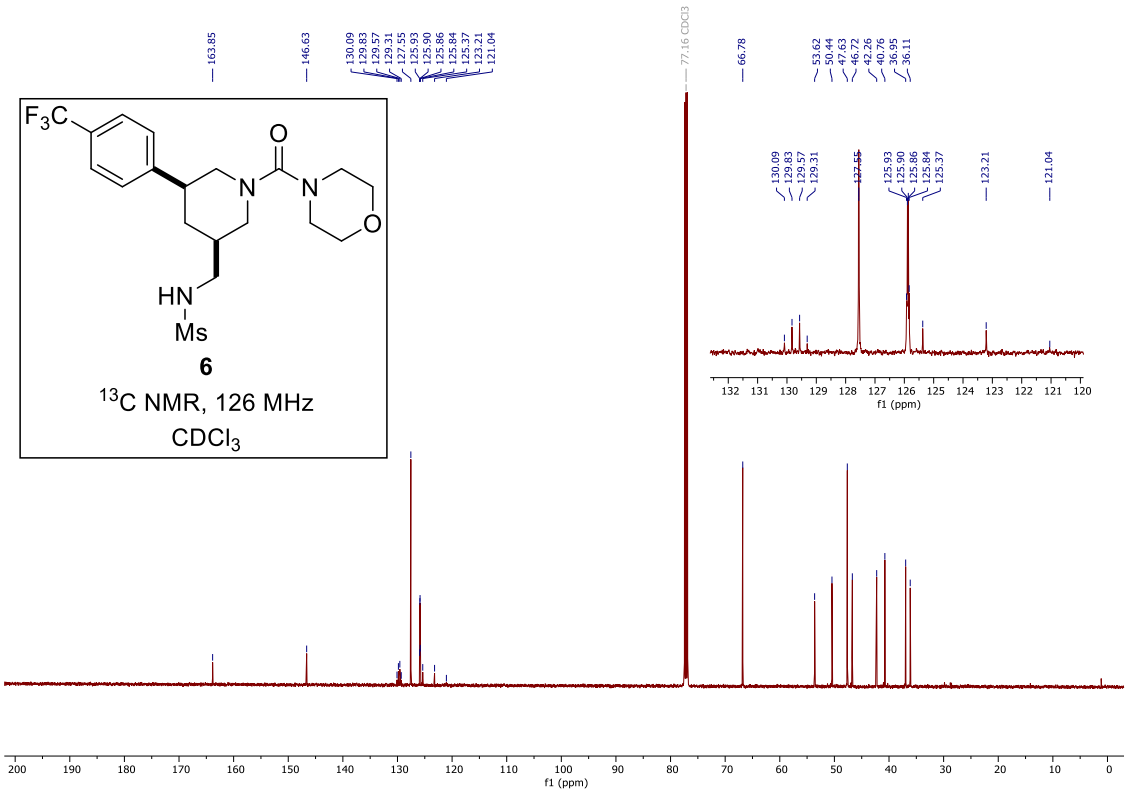


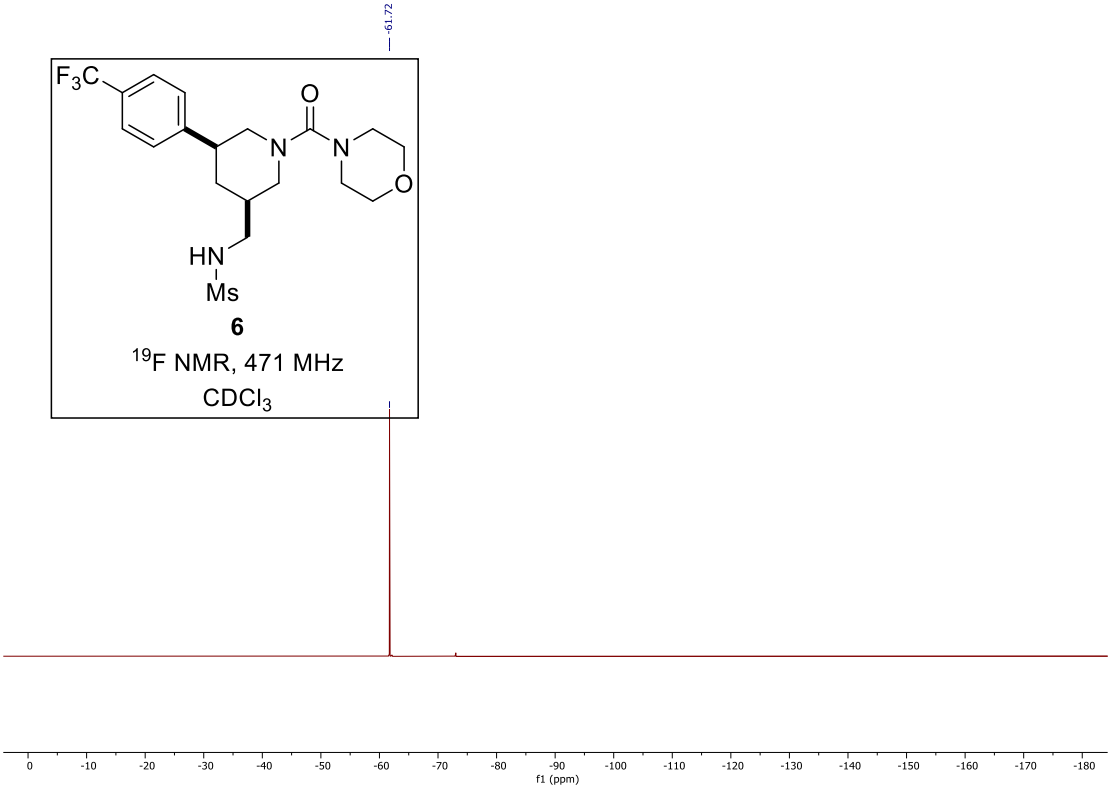


5 (92.7 mg, 0.265 mmol) was dissolved in THF (4 mL) and 1.32 mL of 1 M BH_3·THF (1.32 mmol, 5 equiv.) was added. The solution was heated to 60 °C for 3 h and cooled to ambient temperature, then quenched by the addition of MeOH. The solvent was removed under reduced pressure and 7 mL of MeOH and 7 mL of 6 N HCl was added to the residue. The mixture was heated 60 °C for 3 h and the MeOH was removed under reduced pressure. Water was added to the mixture, which was then made basic (pH ≈ 14) with 6N NaOH.

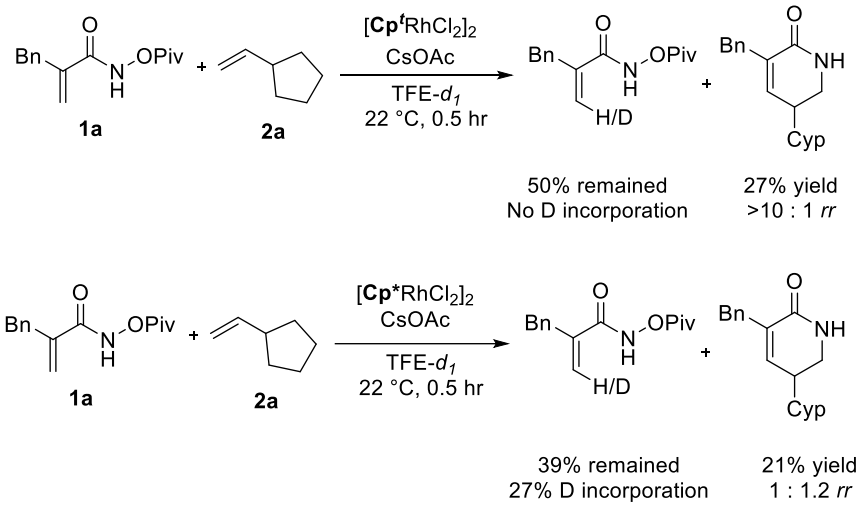
The basic solution was extracted with ethyl acetate and the combined organic extracts were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and 1.3 mL of DCM (0.2 M) was added to the crude mixture. After addition of Et_3N (0.795 mmol, 3 equiv.) and morpholine-4-carbonyl chloride (purchased from sigma and used without purification, 0.530 mmol, 2 equiv.), the reaction mixture was stirred at room temperature for 16 hours. After completion volatiles were removed by rotary evaporator and purified by column chromatography using 5% MeOH in DCM as the eluent to afford product **6**. **Yield**: 63 mg, 53% (over 2 steps), white solid. *dr* = 4.3 : 1 $\mathbf{R_f}$ = 0.24 (5% MeOH in DCM). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60 – 7.57 (m, 2H), 7.35 – 7.31 (m, 2H), 4.46 (t, *J* = 6.5 Hz, 1H), 3.97 – 3.90 (m, 1H), 3.86 – 3.75 (m, 1H), 3.75 – 3.62 (m, 4H), 3.32 – 3.23 (m, 4H), 3.17 – 3.02 (m, 2H), 2.99 (s, 3H), 2.88 (ddt, *J* = 12.2, 7.5, 3.8 Hz, 1H), 2.79 (dd, *J* = 12.7, 11.6 Hz, 1H), 2.52 (dd, *J* = 13.0, 11.4 Hz, 1H), 2.14 – 2.08 (m, 1H), 2.05 – 1.94 (m, 1H), 1.37 (q, *J* = 12.2 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.9, 146.6, 129.7 (q, *J* = 32.5 Hz), 127.6, 125.9 (q, *J* = 3.7 Hz), 124.3 (q, *J* = 272.0 Hz), 66.8, 53.6, 50.4, 47.6, 46.7, 42.3, 40.8, 37.0, 36.1. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -61.7. **IR** ($CDCl_3$, cm^{-1}) *v* 3226, 2923, 2855, 1619, 1419, 1323, 1152, 1113, 1068, 908, 731. **HRMS** (ASAP) m/z $[C_{19}H_{25}F_3N_3O_4S]^-$ ($[M-H]^-$) calculated 448.1518, found 448.1514.




163.85
146.63
130.09
129.83
129.57
129.31
127.55
125.93
125.90
125.86
125.84
125.37
123.21
121.04
77.16 CDCl3
66.78
53.62
50.44
47.63
46.72
42.26
40.76
36.95
36.11
F3C
O
N
N
O
HN
Ms
6
13C NMR, 126 MHz
CDCl3
f1 (ppm)

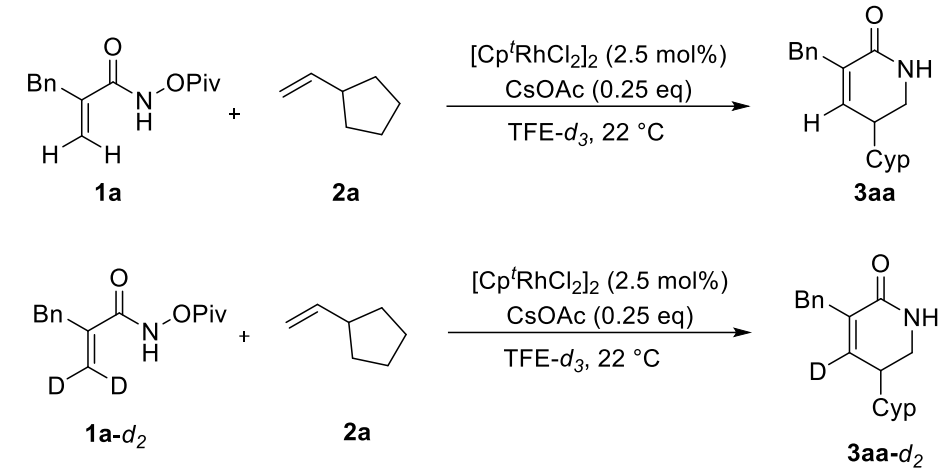

-61.72
F3C
O
N
N
O
HN
Ms
6
19F NMR, 471 MHz
CDCl3
f1 (ppm)

7. Mechanistic Studies

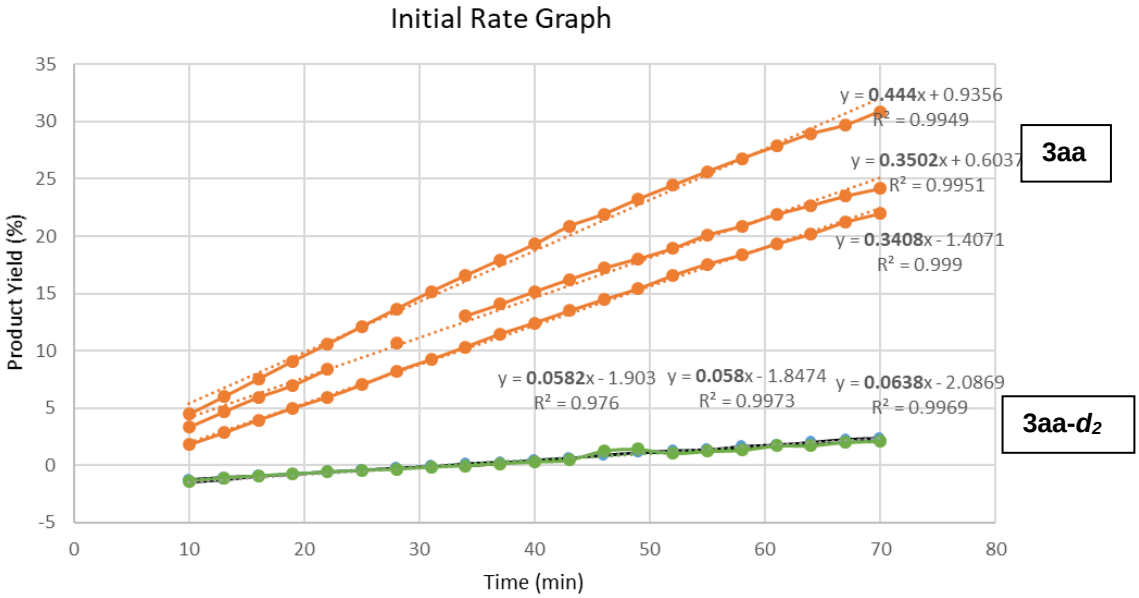


To a 1 dram screw-capped vial with a magnetic stir bar was added 2-benzyl-*N*-(pivaloyloxy)acrylamide (**1a**, 0.10 mmol, 1 equiv), $[Cp^tRhCl_2]_2$ (0.0025 mmol, 2.5 mol%) or $[Cp^*RhCl_2]_2$ (0.0025 mmol, 2.5 mol%) and cesium acetate (0.025 mmol, 0.25 equiv) and dissolved in 0.33 mL of TFE-d_1. Vinyl cyclopentane (2a, 0.20 mmol, 2 equiv) was added to the vial and the cap was screwed on and the reaction was stirred at 22 °C for 30 minutes. The reaction mixture was quenched by saturated $NaHCO_3$ solution and extracted three times with dichloromethane. The combined organic layer was dried over $MgSO_4$ and filtered through celite. The filtrate was concentrated by rotary evaporation and the crude mixture was analyzed by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard. When $[Cp^tRhCl_2]_2$ was used as a catalyst, no deuterium incorporation was observed in the recovered 2-benzyl-*N*-(pivaloyloxy)acrylamide. In contrast, 27% of deuterium incorporation was observed in the case of $[Cp^*RhCl_2]_2$.

KIE determined from two parallel reactions

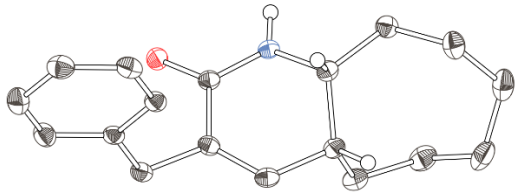


KIE was measured from two separated reactions, one with **1a** containing a C-H bond and one with an analogous C-D bond (**1a**-d_2). **1a** (or **1a**-d_2) (0.15 mmol, 1 equiv), $[Cp^tRhCl_2]_2$ (0.00375 mmol, 2.5 mol%), cesium acetate (0.0375 mmol, 0.25 equiv) and 1,3,5-trimethoxybenzen (0.05 mmol, internal standard) was dissolved in 0.5 mL of TFE-d_3 and transferred to J-young NMR tube. Vinyl cyclopentane (**2a**, 0.30 mmol, 2 equiv) was added to the NMR tube directly and reaction progress was monitored by *in situ* ^{1}H NMR at 22 °C. KIE value was calculated by comparing the initial reaction rate (slope) of each reaction (repeated 3 times each). Observed primary KIE (K_H / K_D) value of 6.31 suggests C-H bond cleavage occurs during the turnover limiting step.

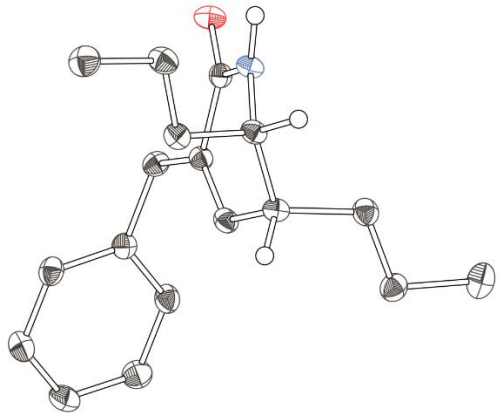


8. X-ray Crystal Structure

Single crystal X-ray diffraction was performed at the Shared Materials Characterization Laboratory at Columbia University. Use of the SMCL was made possible by funding from Columbia University. Data for all compounds was collected on an Agilent SuperNova diffractometer using mirror-monochromated Cu Kα or Mo Kα radiation. Data collection, integration, scaling (ABSPACK) and absorption correction (face-indexed Gaussian integration or numeric analytical methods) were performed in CrysAlisPro. Structure solution was performed using ShelXT. Subsequent refinement was performed by full-matrix least-squares on F2 in ShelXL. For **3aq** and **3av**, all non-H atoms were located in the initial solutions and refined with free anisotropic ADPs. C-H hydrogens were placed in calculated positions and refined with riding isotropic ADPs and coordinates. N-H hydrogens were refined freely with isotropic ADPs. Olex2 was used for viewing and to prepare CIF files. PLATON CheckCIF. ORTEP graphics were prepared in CrystalMaker. Thermal ellipsoids are rendered at the 50% probability level.



3aq: Crystallized by vapor diffusion of pentane into benzene. Black, carbon; blue, nitrogen; red, oxygen; white spheres, hydrogen. Most C-H hydrogens are omitted for clarity.



3av: Crystallized by vapor diffusion of pentane into benzene. Black, carbon; blue, nitrogen; red, oxygen; white spheres, hydrogen. Most C-H hydrogens are omitted for clarity.

Compound	3aq	3av
Formula	$C_{18}H_{23}NO$	$C_{18}H_{25}NO$
MW	269.37	271.39
Space group	$P2_1/c$	P-1
a (Å)	10.2414(2)	7.3848(3)
b (Å)	5.75070(10)	9.6884(5)
c (Å)	24.6727(6)	11.6917(7)
α (°)	90	101.377(5)
β (°)	93.685(2)	103.736(4)
γ (°)	90	98.276(4)
V (Å^3)	1450.10(5)	780.46(7)
Z	4	2
ρ_{calc} (g cm^{-3})	1.234	1.155
T (K)	100	100
λ (Å)	1.54184	.71073
$2\theta_{min}$, $2\theta_{max}$	7, 146	7, 59
Nref	8619	10677
R(int), R(σ)	.0539, .0508	.0455, .0605
μ(mm^{-1})	0.582	0.070
Size (mm)	.21 x .06 x .03	.32 x .19 x .10
T_{max} / T_{min}	1.26	1.39
Data	2888	3780
Restraints	0	0
Parameters	185	187
R_1(obs)	0.0540	0.0532
wR_2(all)	0.1485	0.1226
S	1.042	1.037
Peak, hole (e$^-$ Å^{-3})	.34, -.25	.28, -.26

9. References

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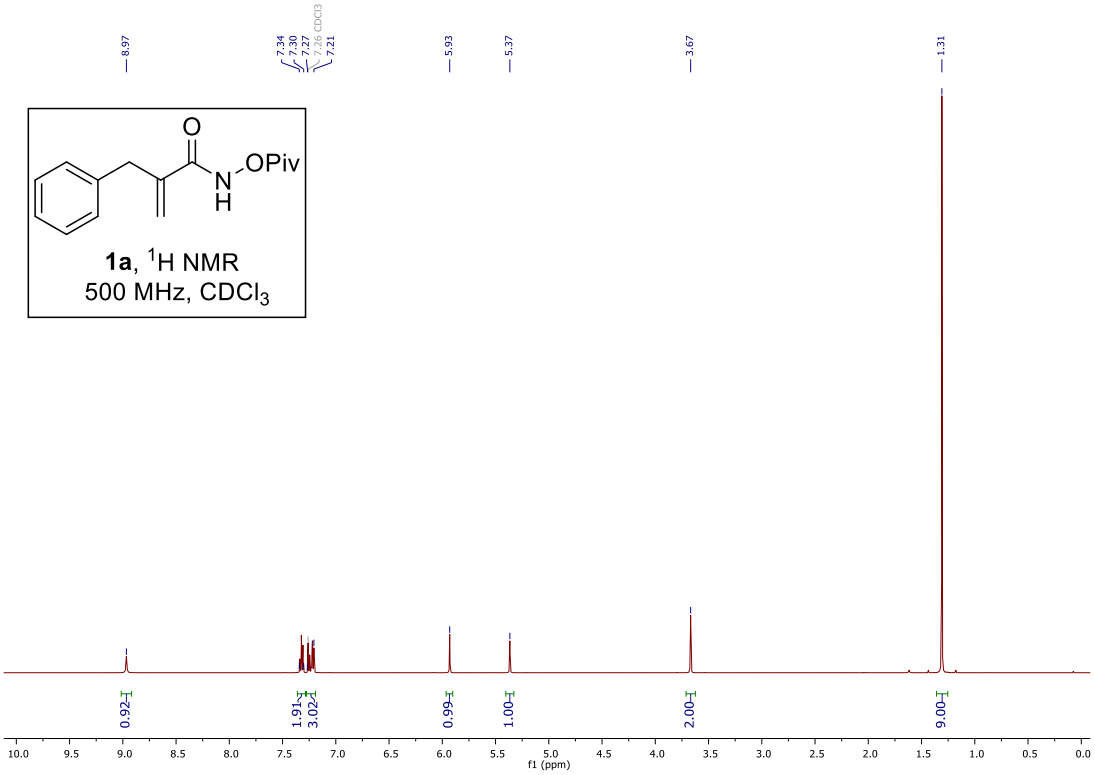
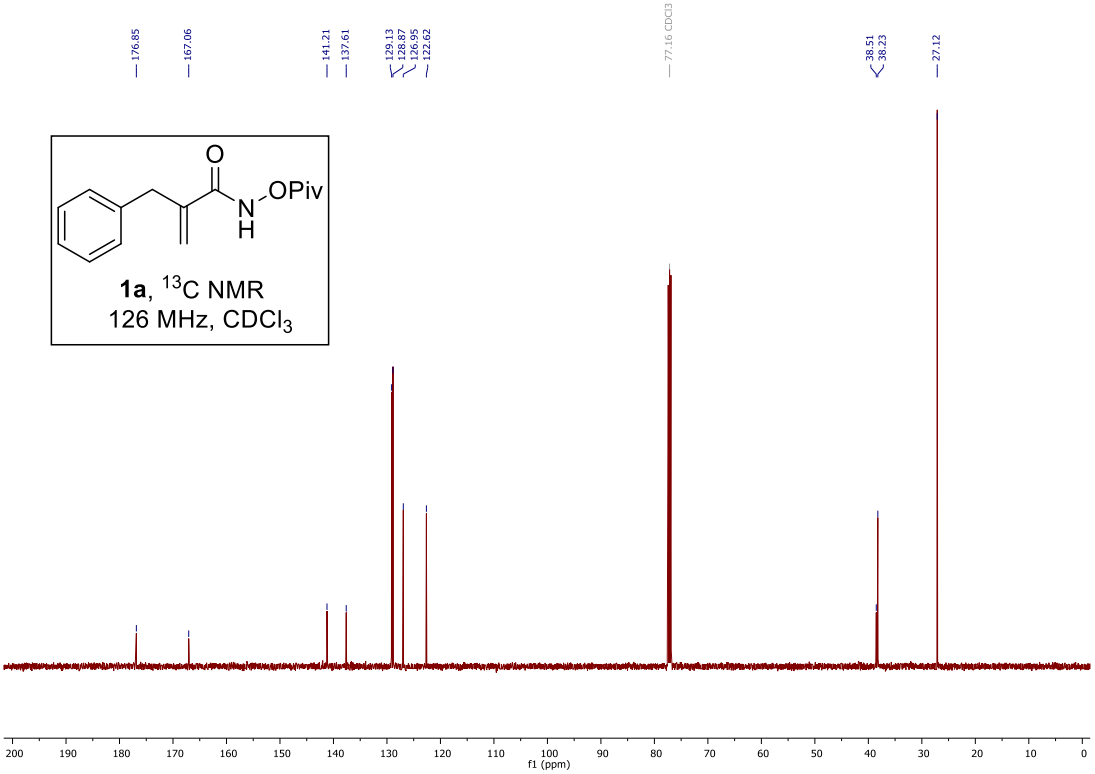
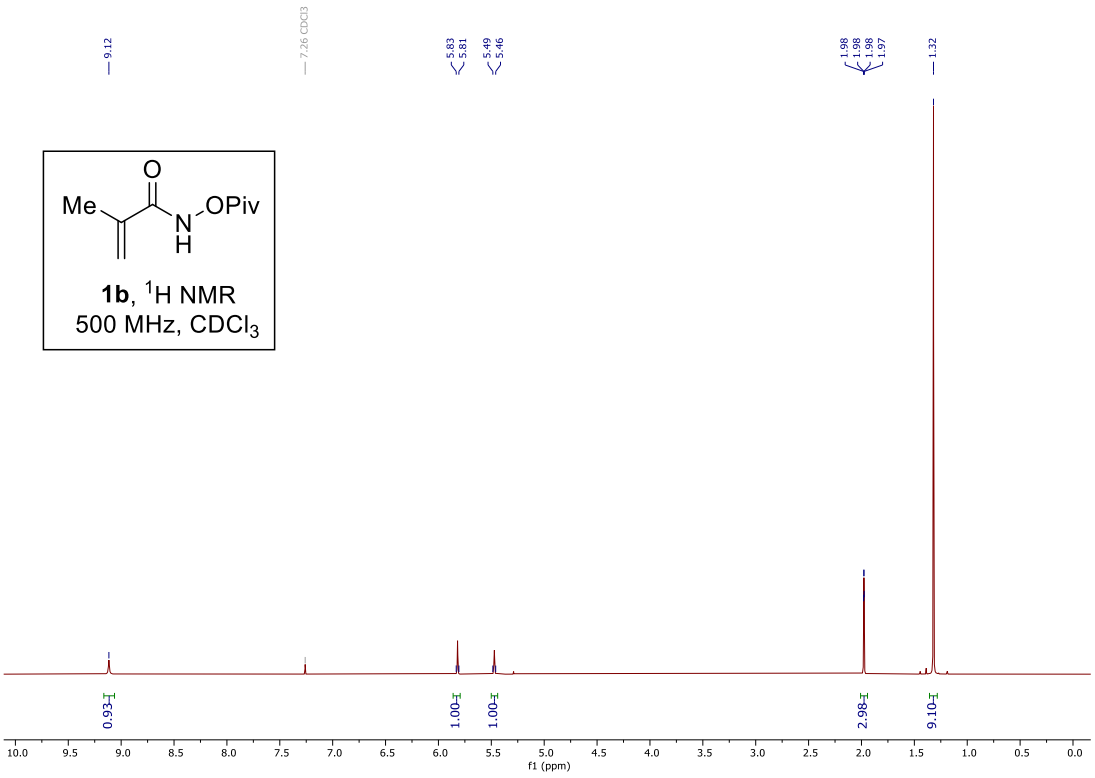
10. NMR Spectra



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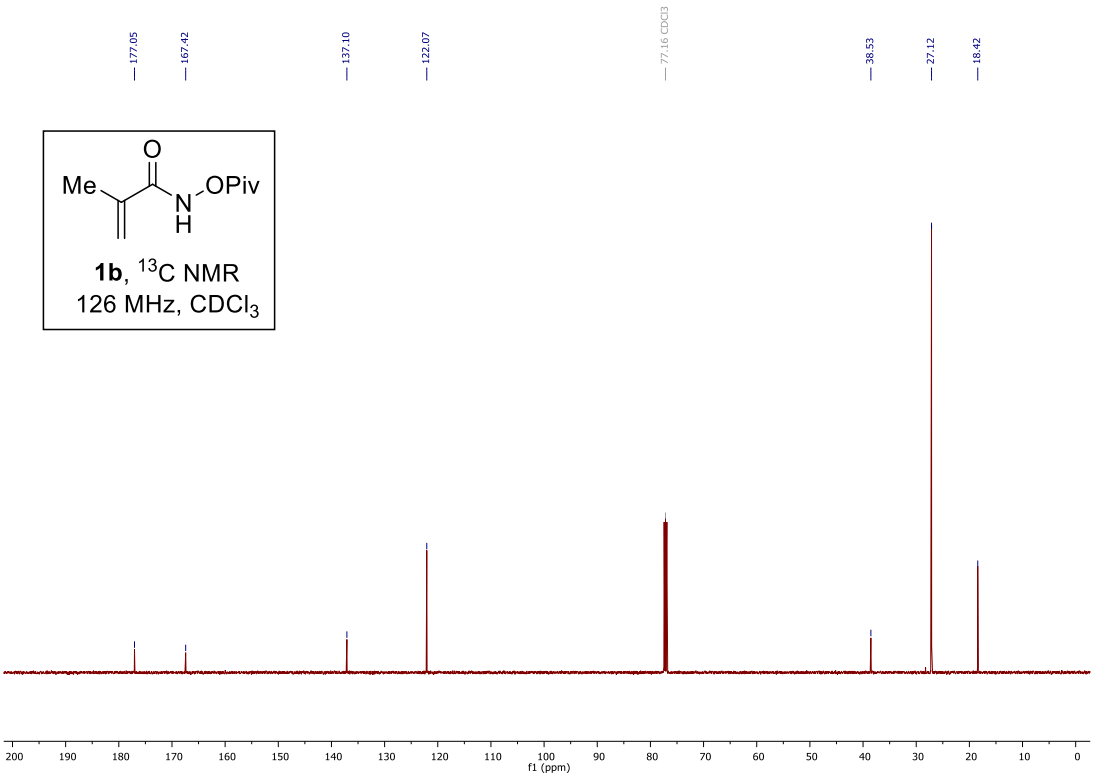
5.83
5.81
5.49
5.46
1.98
1.98
1.98
1.97
1.32
Me
O
N
H
OPiv
1b, 1H NMR
500 MHz, CDCl3
0.93
1.00
1.00
2.98
9.10
f1 (ppm)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122.07
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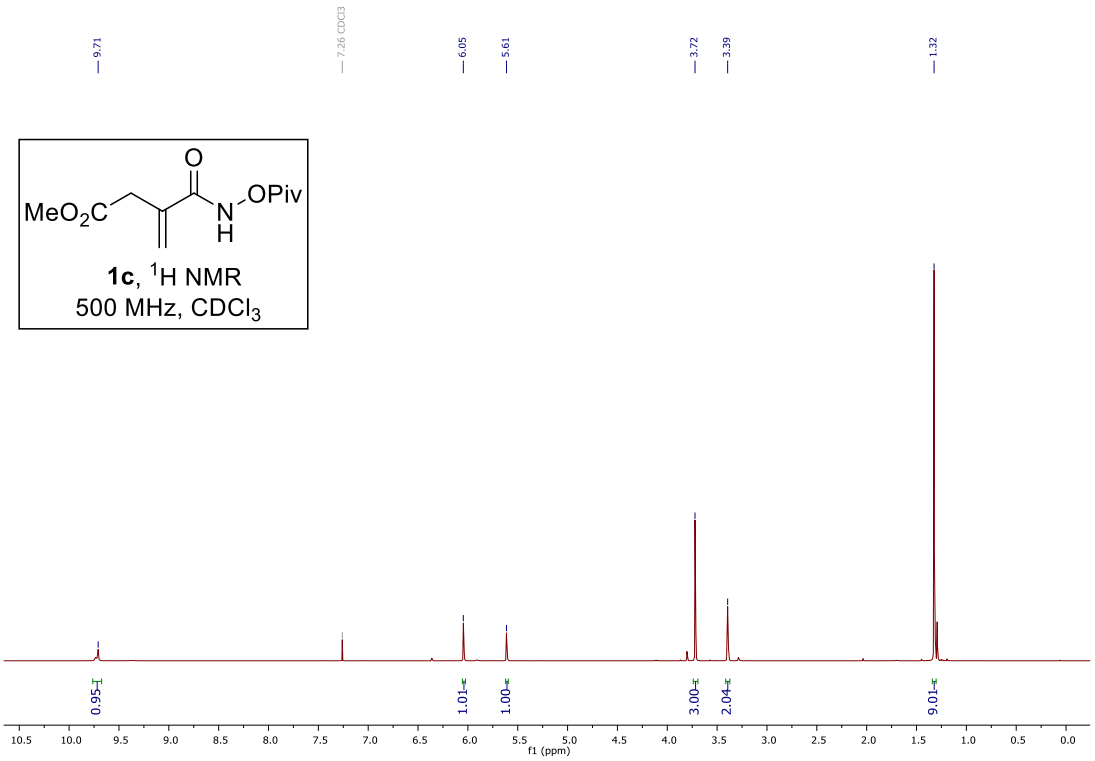
O
N
H
OPiv
1b, 13C NMR
126 MHz, CDCl3
f1 (ppm)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O
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500 MHz, CDCl3
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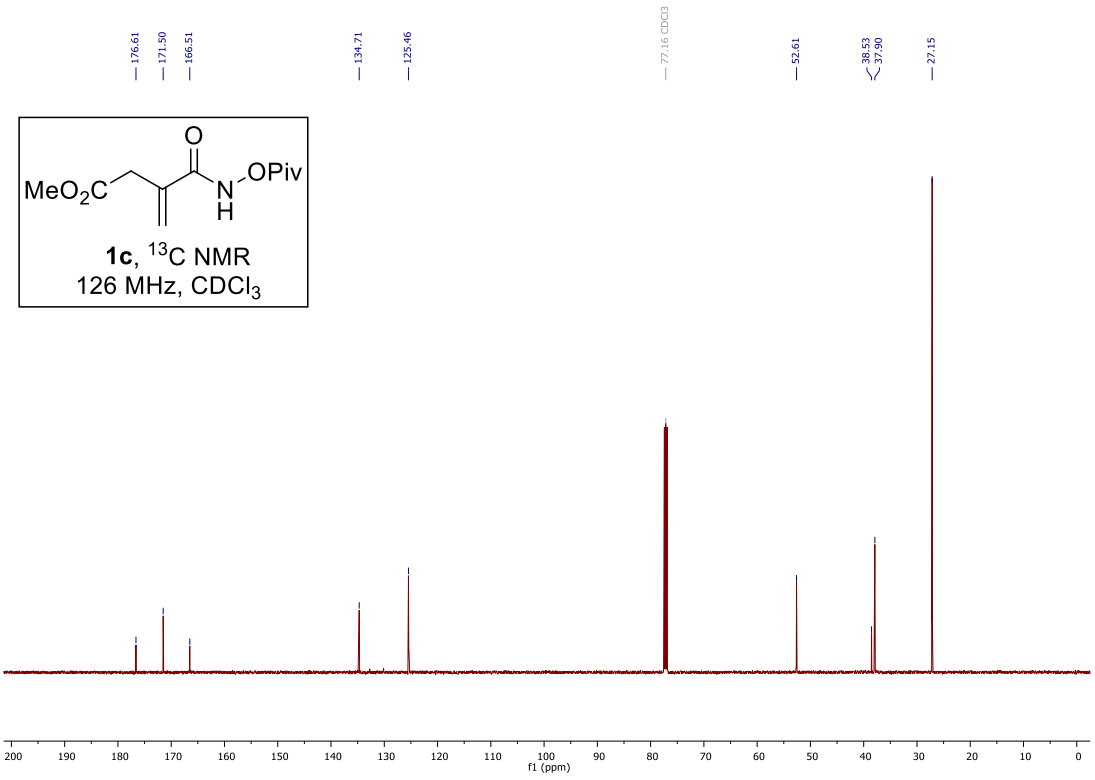
1.00
3.00
2.04
9.01
f1 (ppm)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171.50
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134.71
125.46
77.16 CDCl3
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27.15
MeO2C
O
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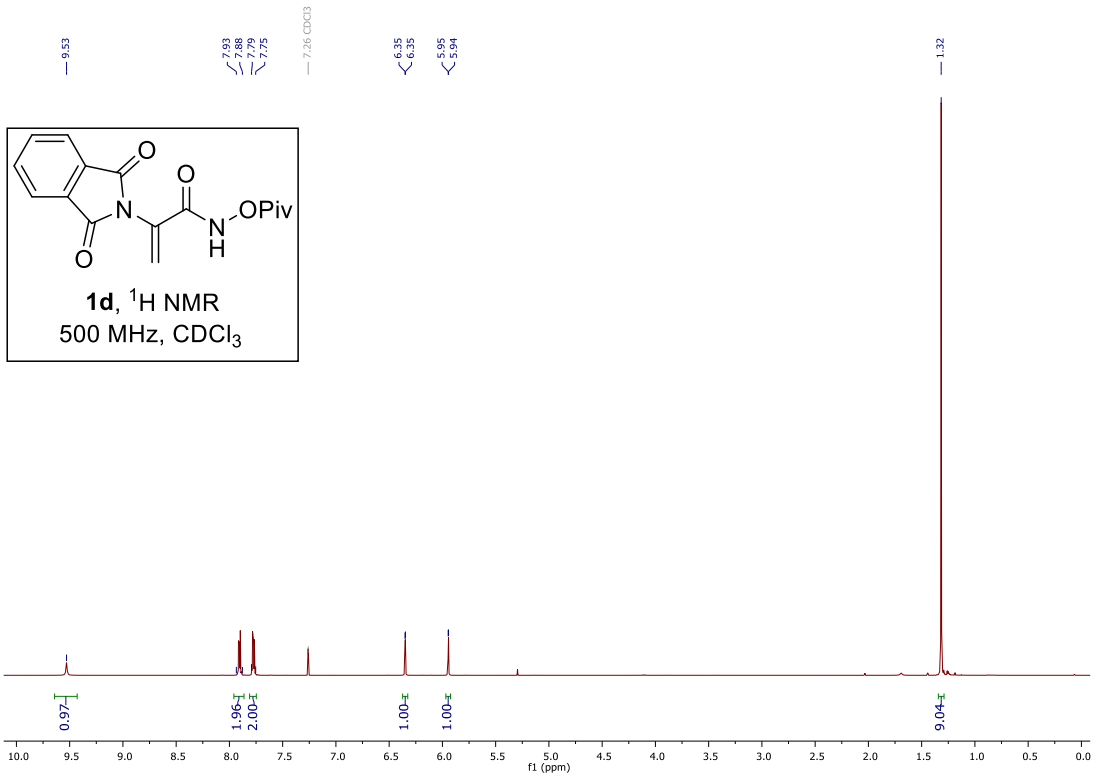
H
OPiv
1c, 13C NMR
126 MHz, CDCl3
f1 (ppm)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7.93
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7.75
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6.35
6.35
5.95
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O
O
N
OPiv
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H
O
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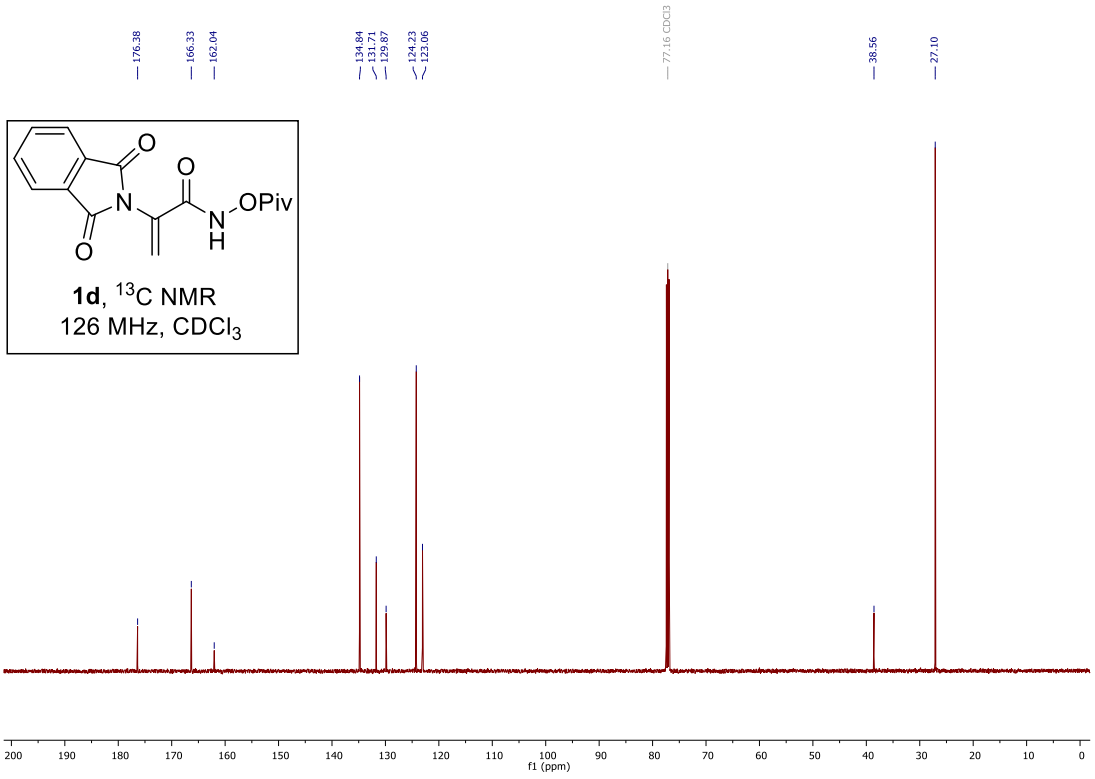
1.00
9.04
f1 (ppm)


176.38
166.33
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134.84
131.71
129.87
124.23
123.06
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O
O
N
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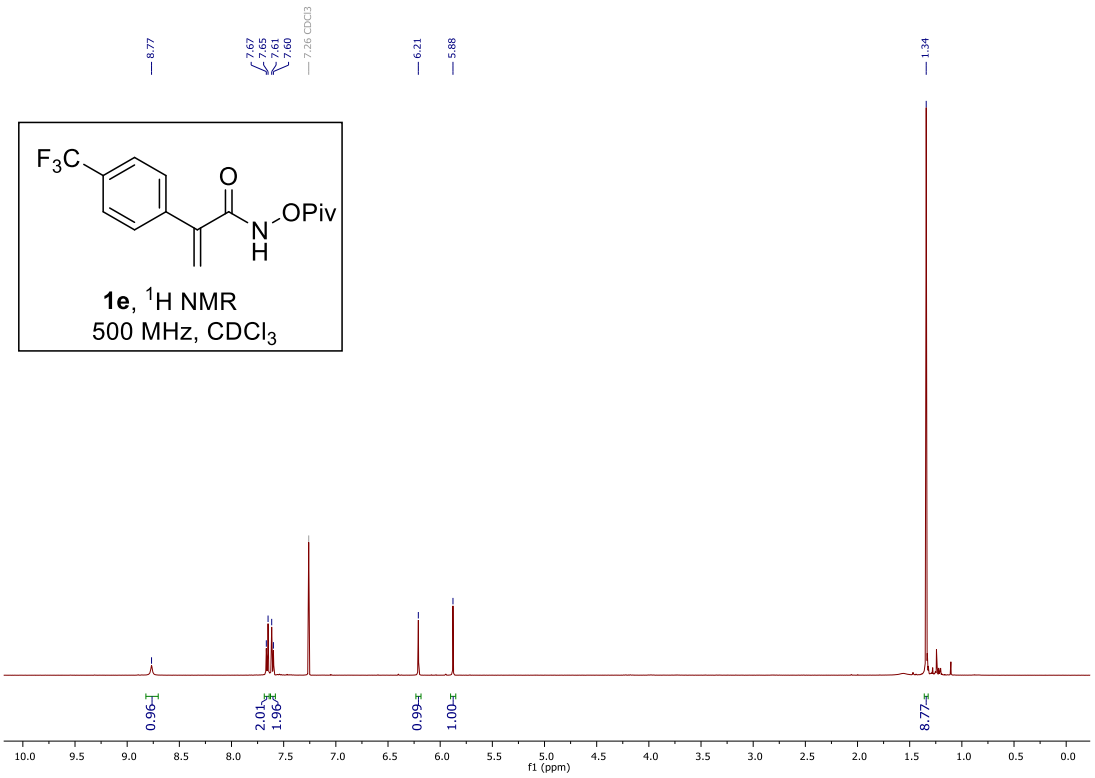
N
H
O
1d, 13C NMR
126 MHz, CDCl3
f1 (ppm)


F3C
O
N
H
OPiv
1e, 1H NMR
500 MHz, CDCl3
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7.67
7.65
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5.88
1.34
0.96
2.01
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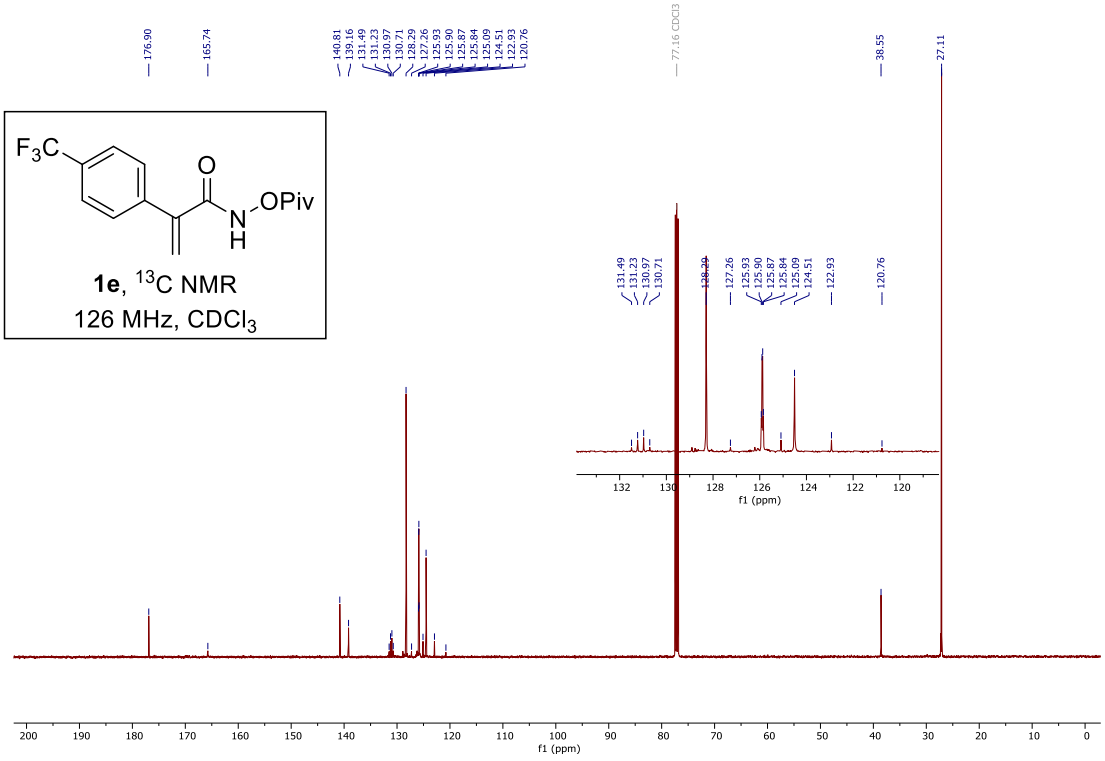
0.99
1.00
8.77
f1 (ppm)


F3C
O
N
H
OPiv
1e, 13C NMR
126 MHz, CDCl3
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140.81
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131.23
130.97
130.71
128.29
127.26
125.93
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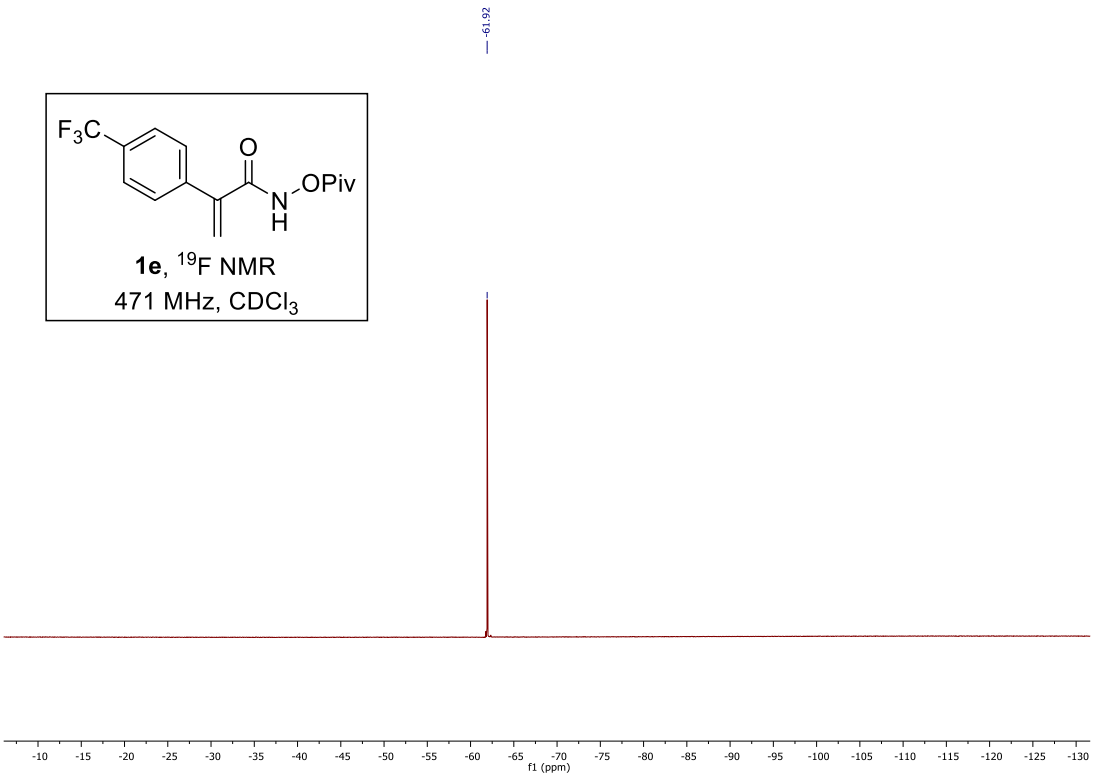
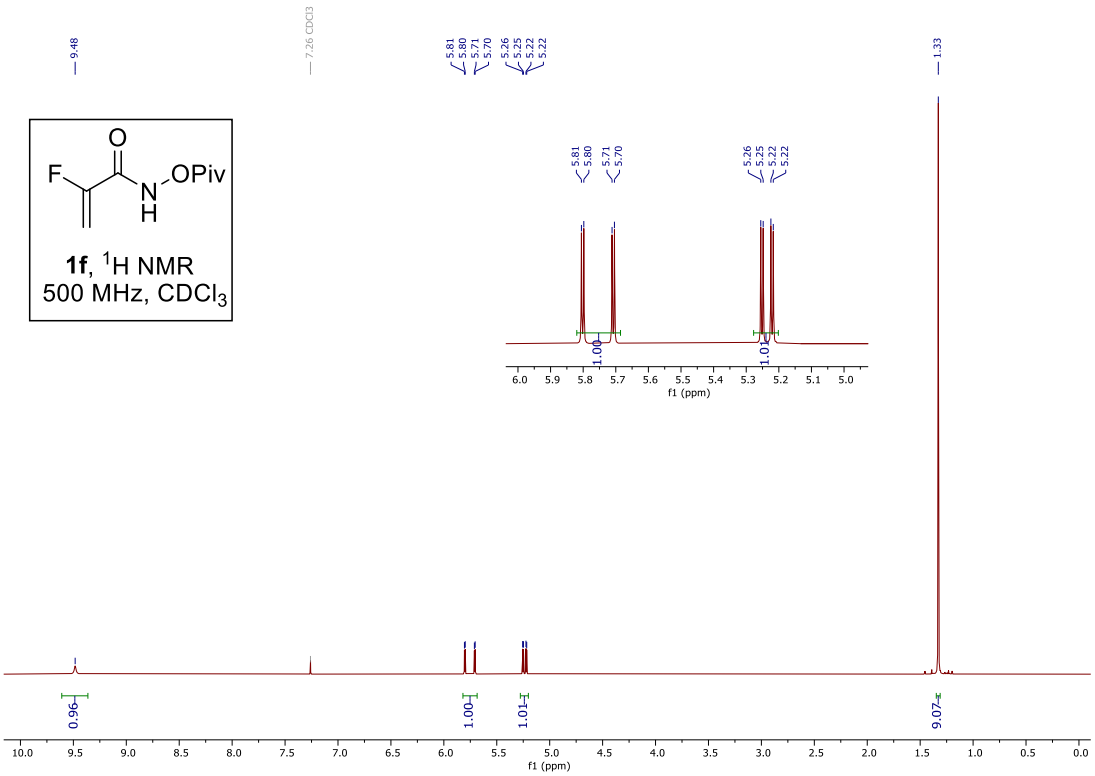
27.11
f1 (ppm)


-61.92
F3C
O
N
H
OPiv
1e, 19F NMR
471 MHz, CDCl3
-10 -15 -20 -25 -30 -35 -40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130
f1 (ppm)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5.22
5.22
1.33
F
O
N
H
OPiv
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f1 (ppm)
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1.00
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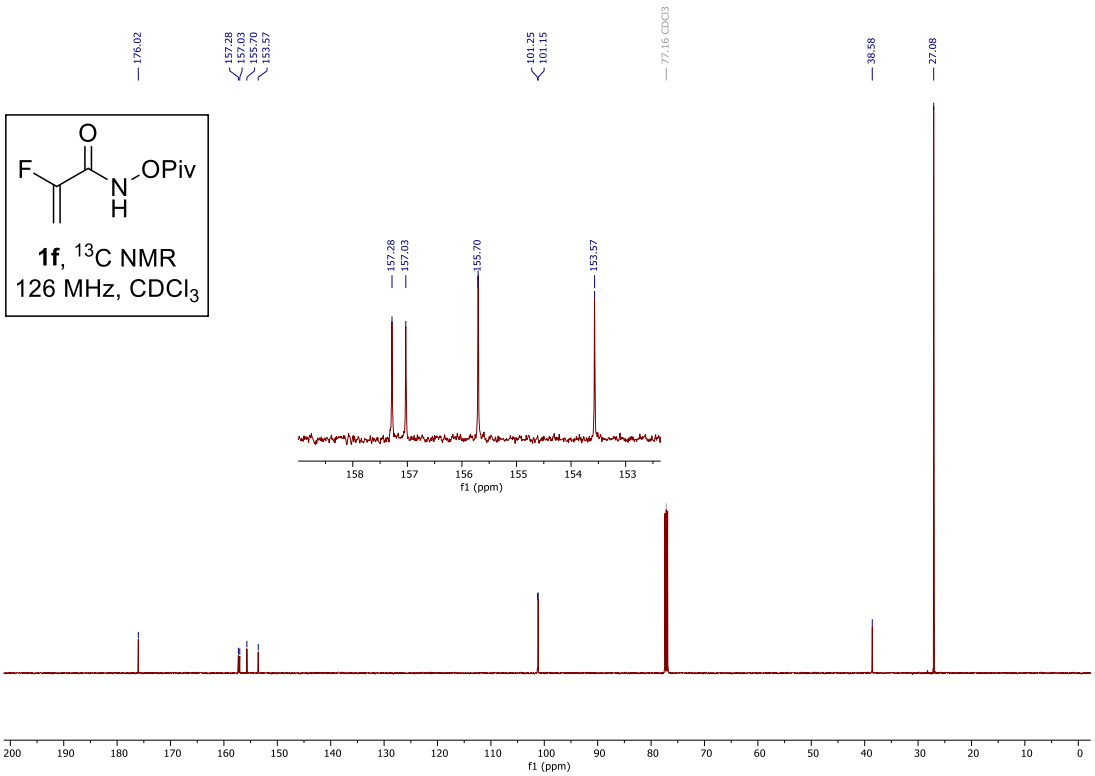
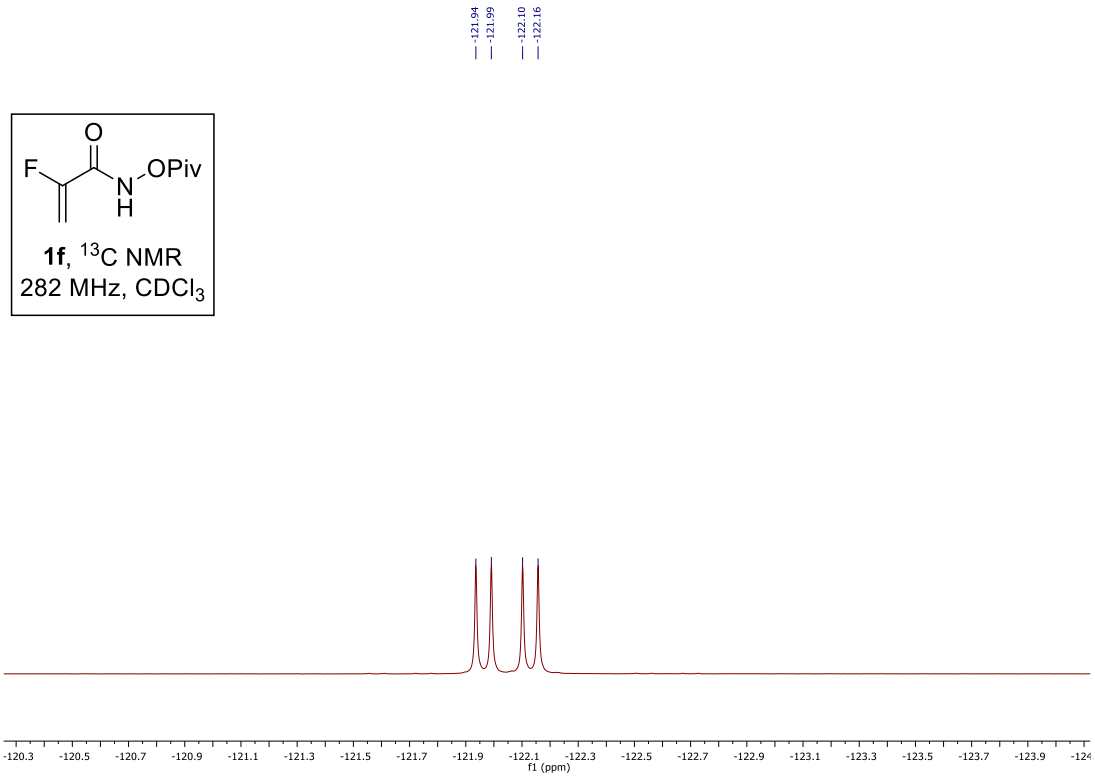
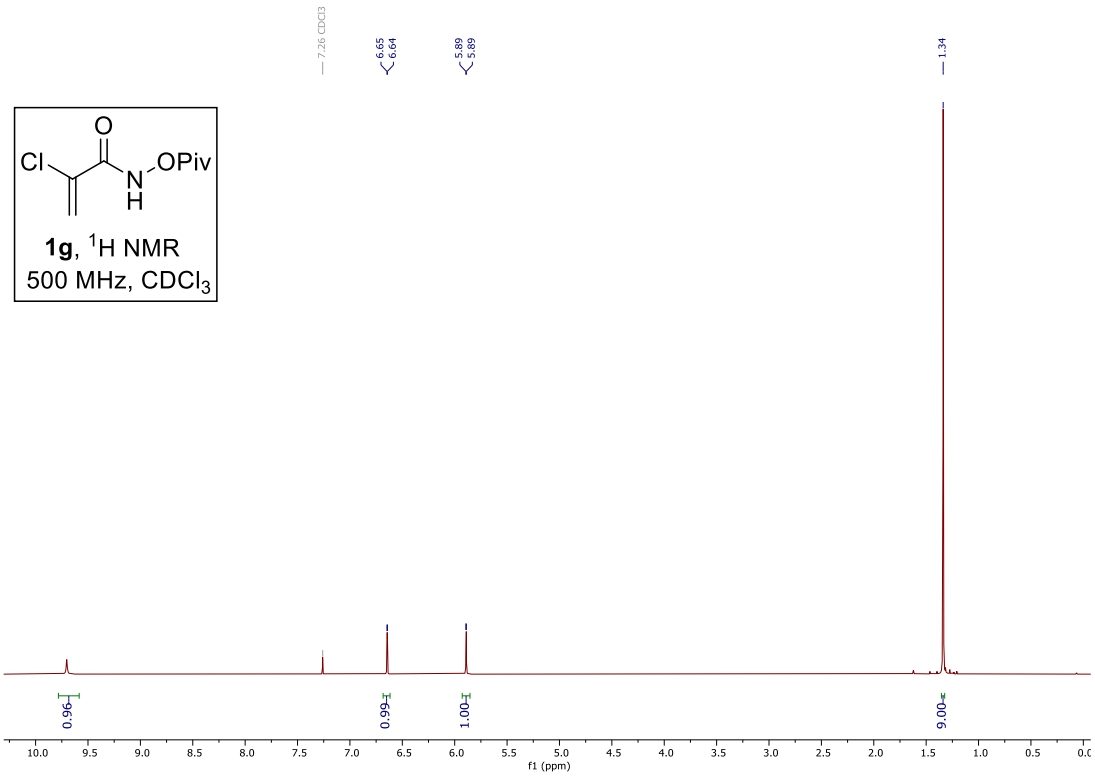
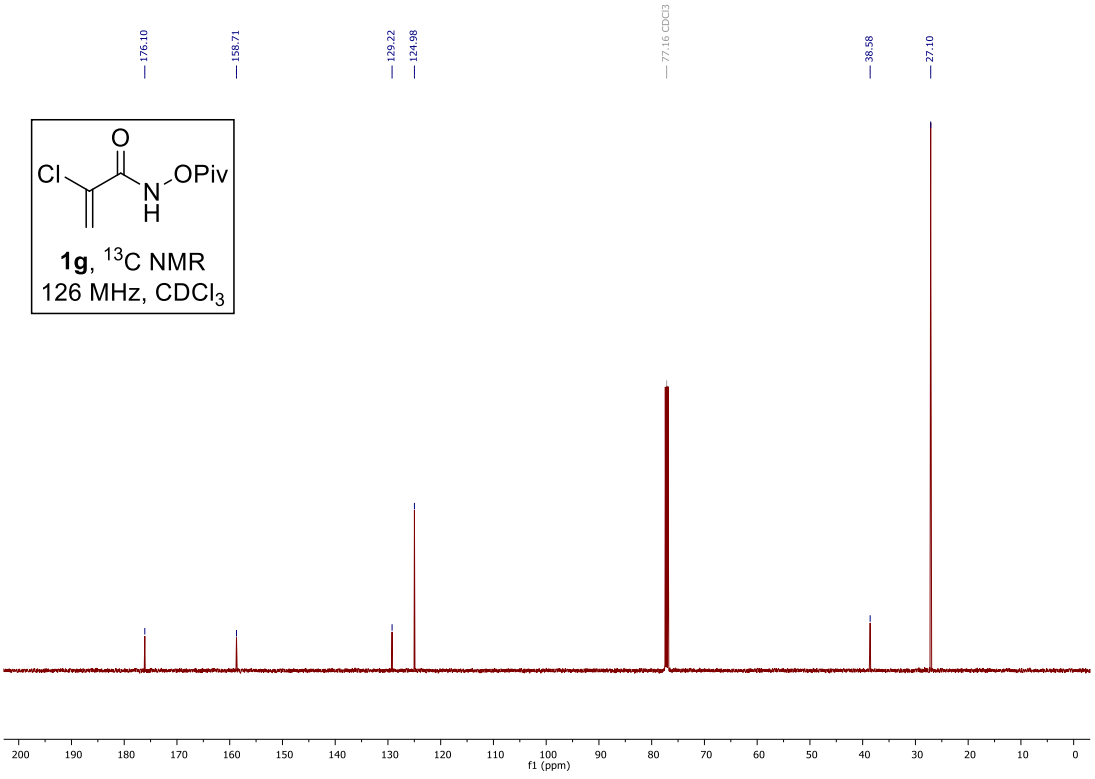
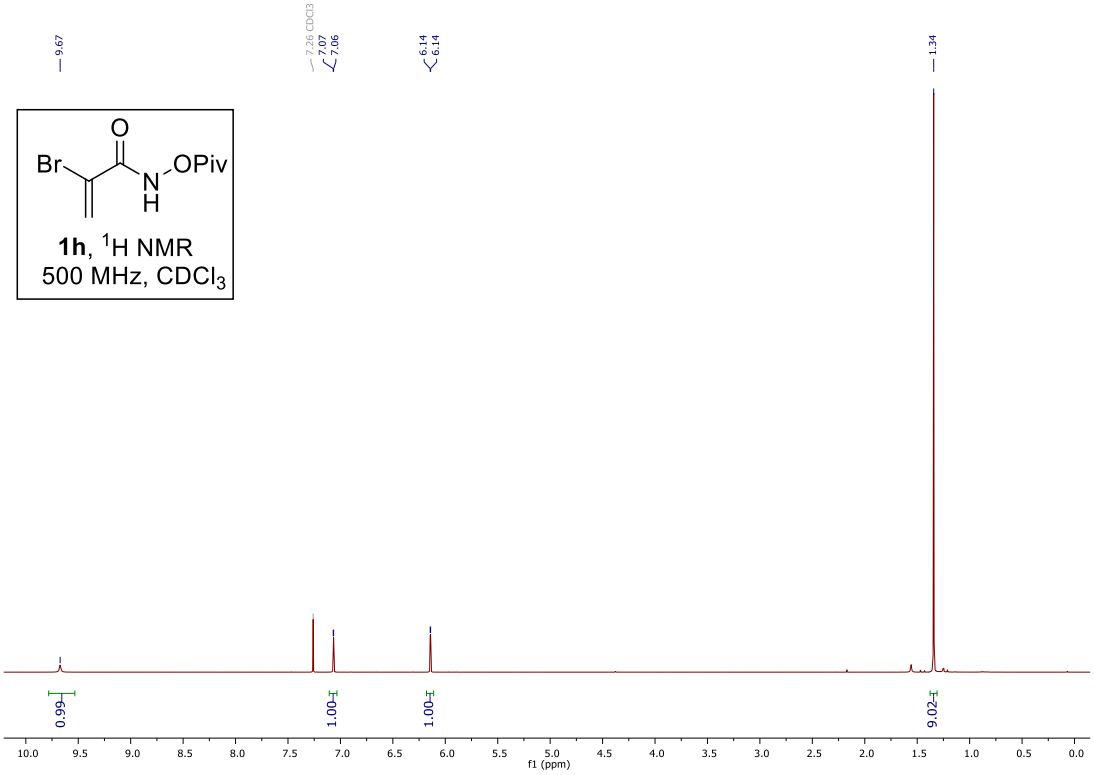
f1 (ppm)

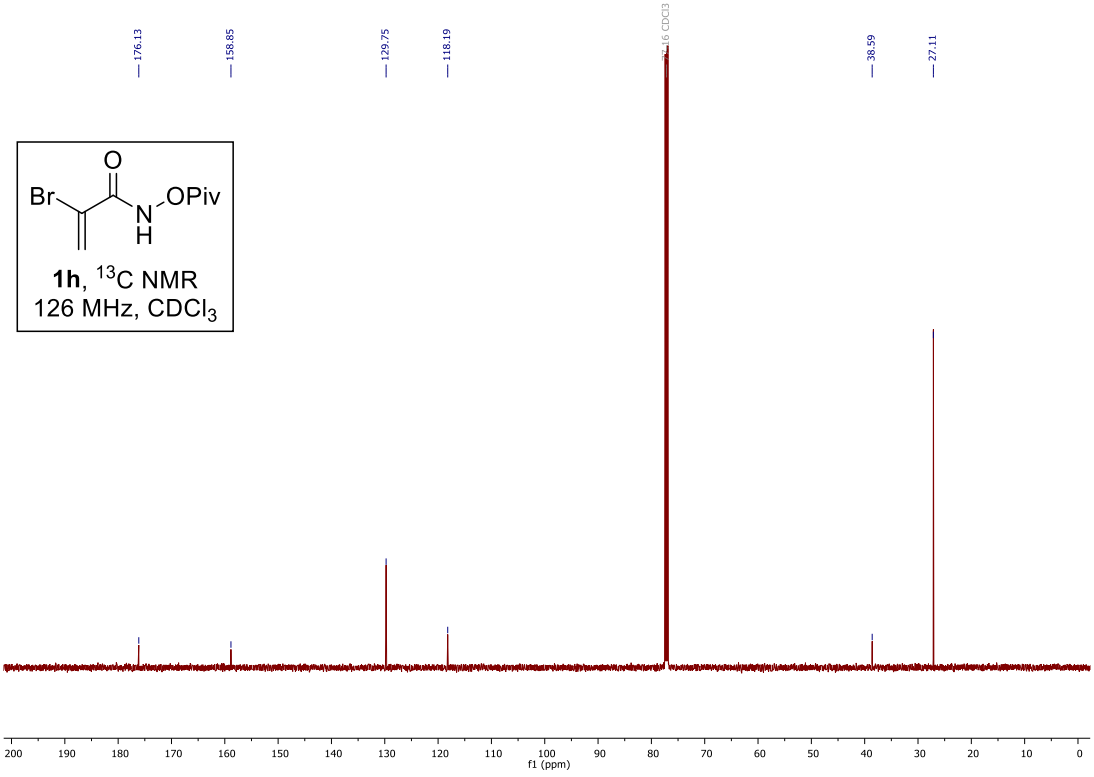

176.02
157.28
157.03
155.70
153.57
101.25
101.15
77.16 CDCl3
38.58
27.08
F
O
N
H
OPiv
1f, 13C NMR
126 MHz, CDCl3
157.28
157.03
155.70
153.57
f1 (ppm)
f1 (ppm)

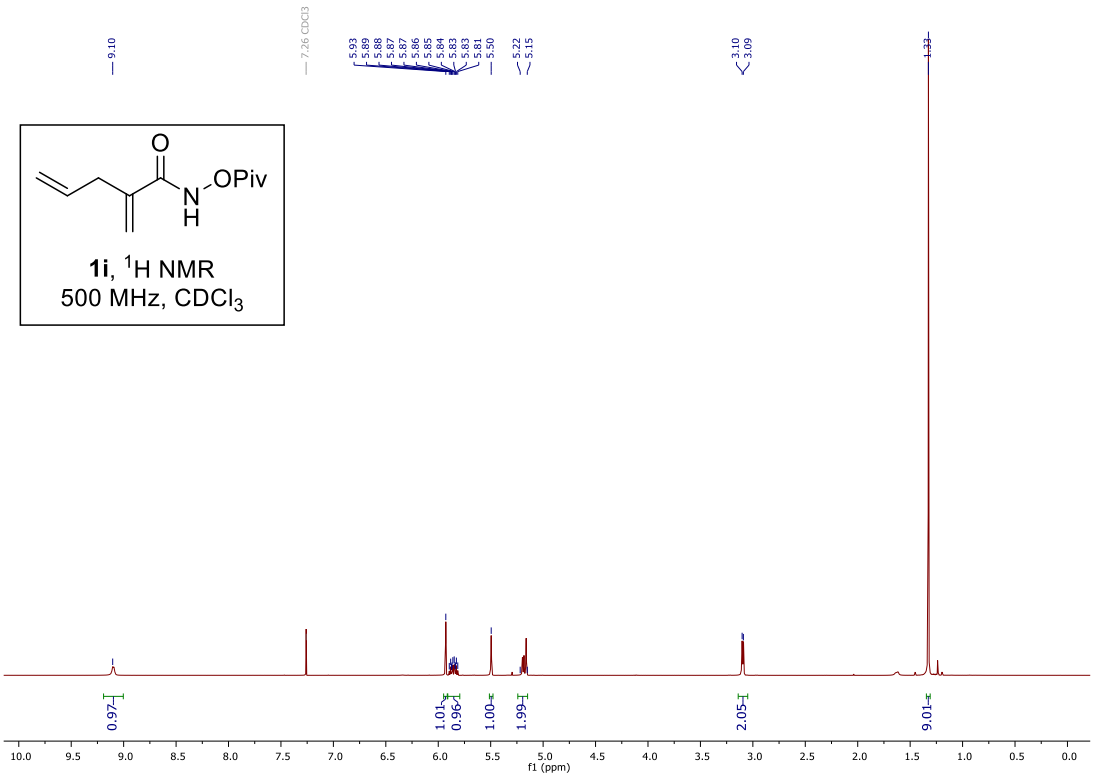

-121.94
-121.99
-122.10
-122.16
O
F
N
H
OPiv
1f, 13C NMR
282 MHz, CDCl3
-120.3
-120.5
-120.7
-120.9
-121.1
-121.3
-121.5
-121.7
-121.9
-122.1
-122.3
-122.5
-122.7
-122.9
-123.1
-123.3
-123.5
-123.7
-123.9
f1 (ppm)

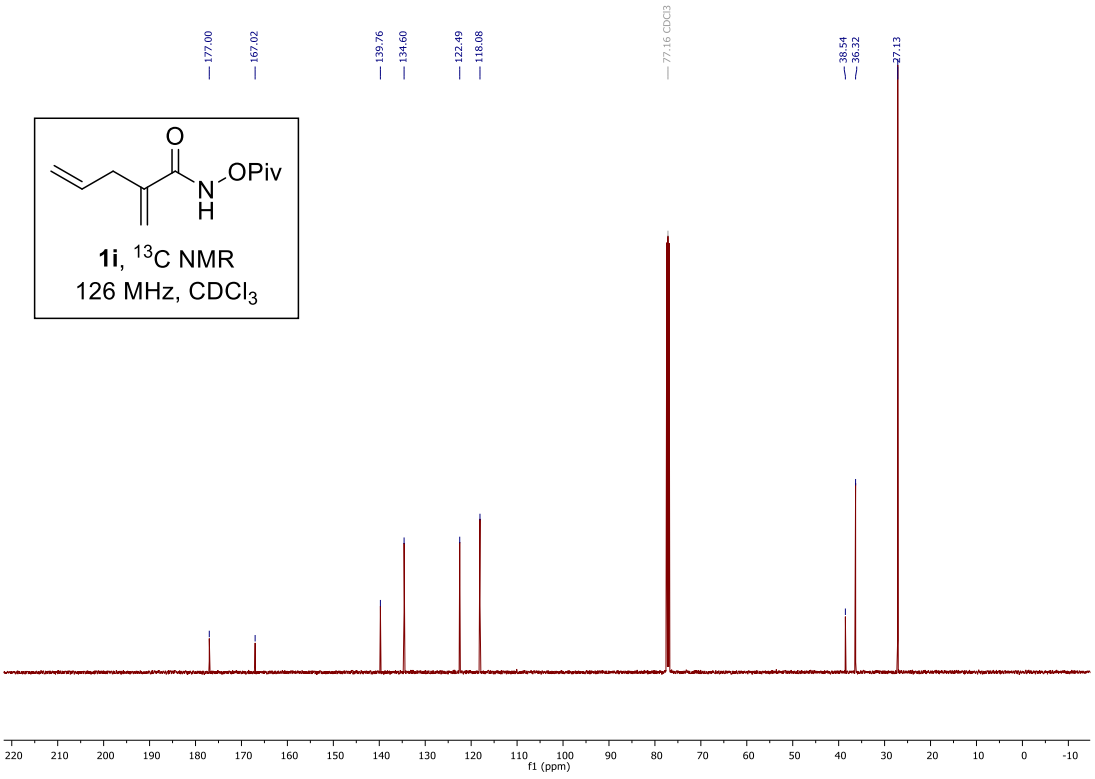

7.26 CDCl3
6.65
6.64
5.89
5.89
1.34
Cl
O
N
H
OPiv
1g, 1H NMR
500 MHz, CDCl3
0.96
0.99
1.00
9.00
f1 (ppm)

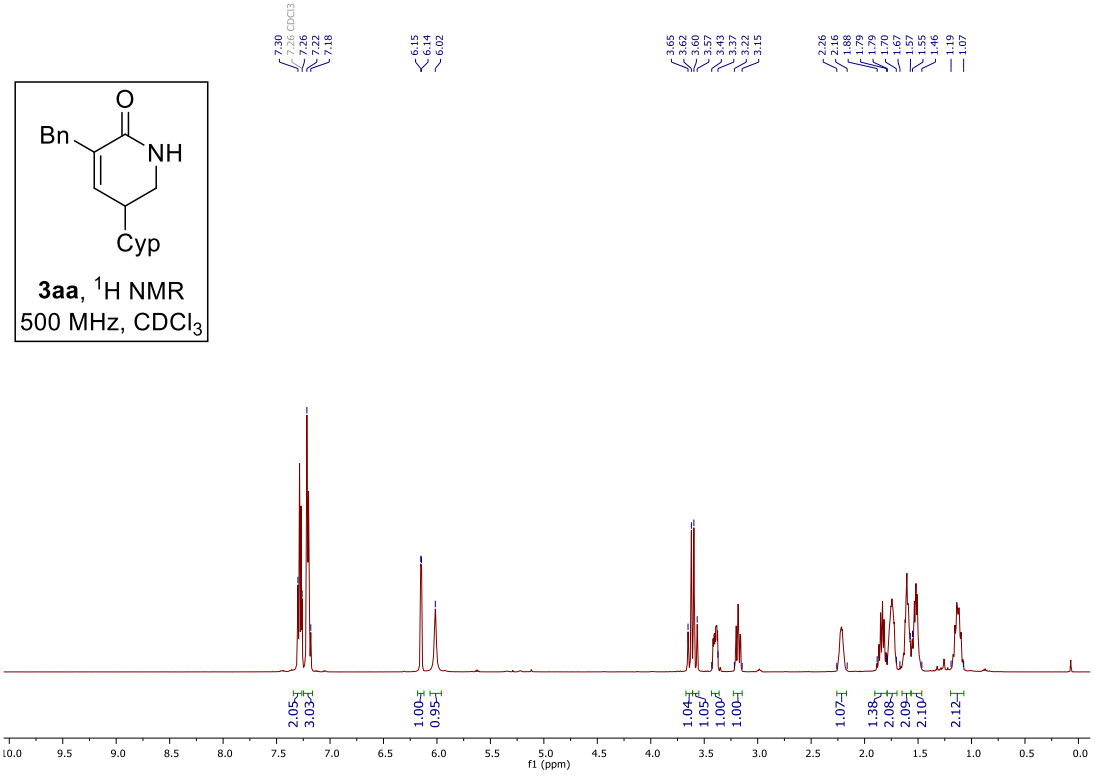

176.10
158.71
129.22
124.98
77.16 CDCl3
38.58
27.10
Cl
O
N
H
OPiv
1g, 13C NMR
126 MHz, CDCl3
f1 (ppm)

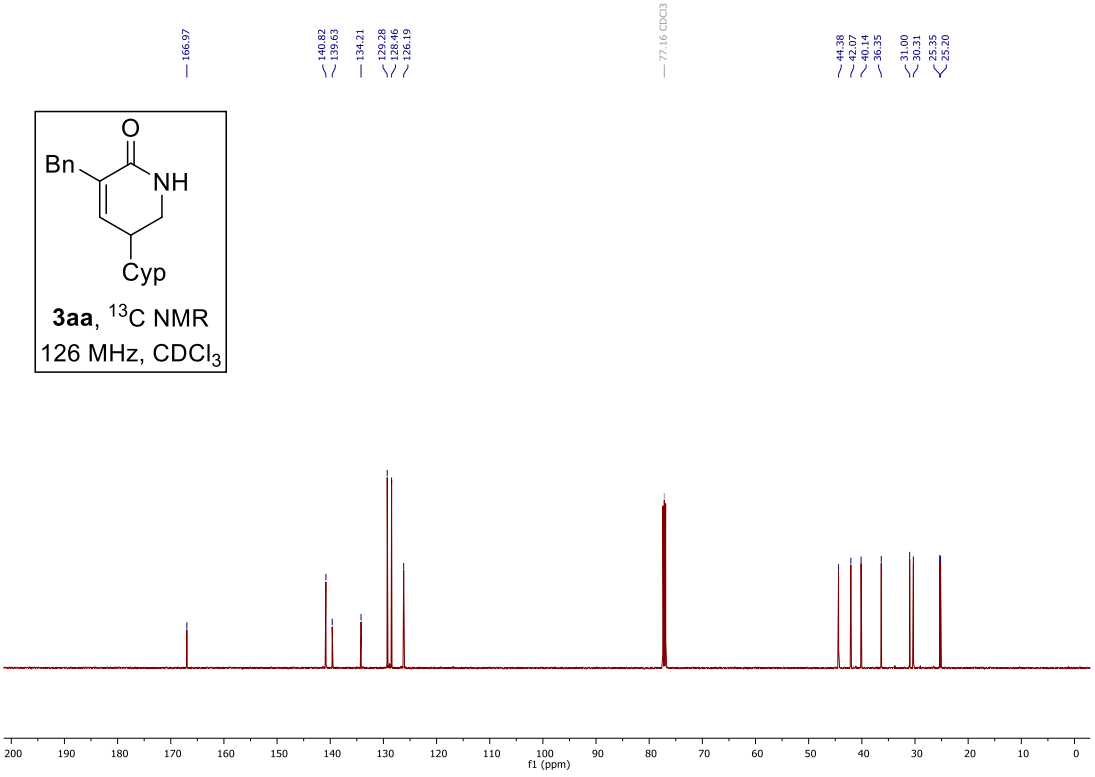

9.67
7.26 CDCl3
7.07
7.06
6.14
6.14
1.34
Br
O
N
H
OPiv
1h, 1H NMR
500 MHz, CDCl3
0.99
1.00
1.00
9.02
f1 (ppm)

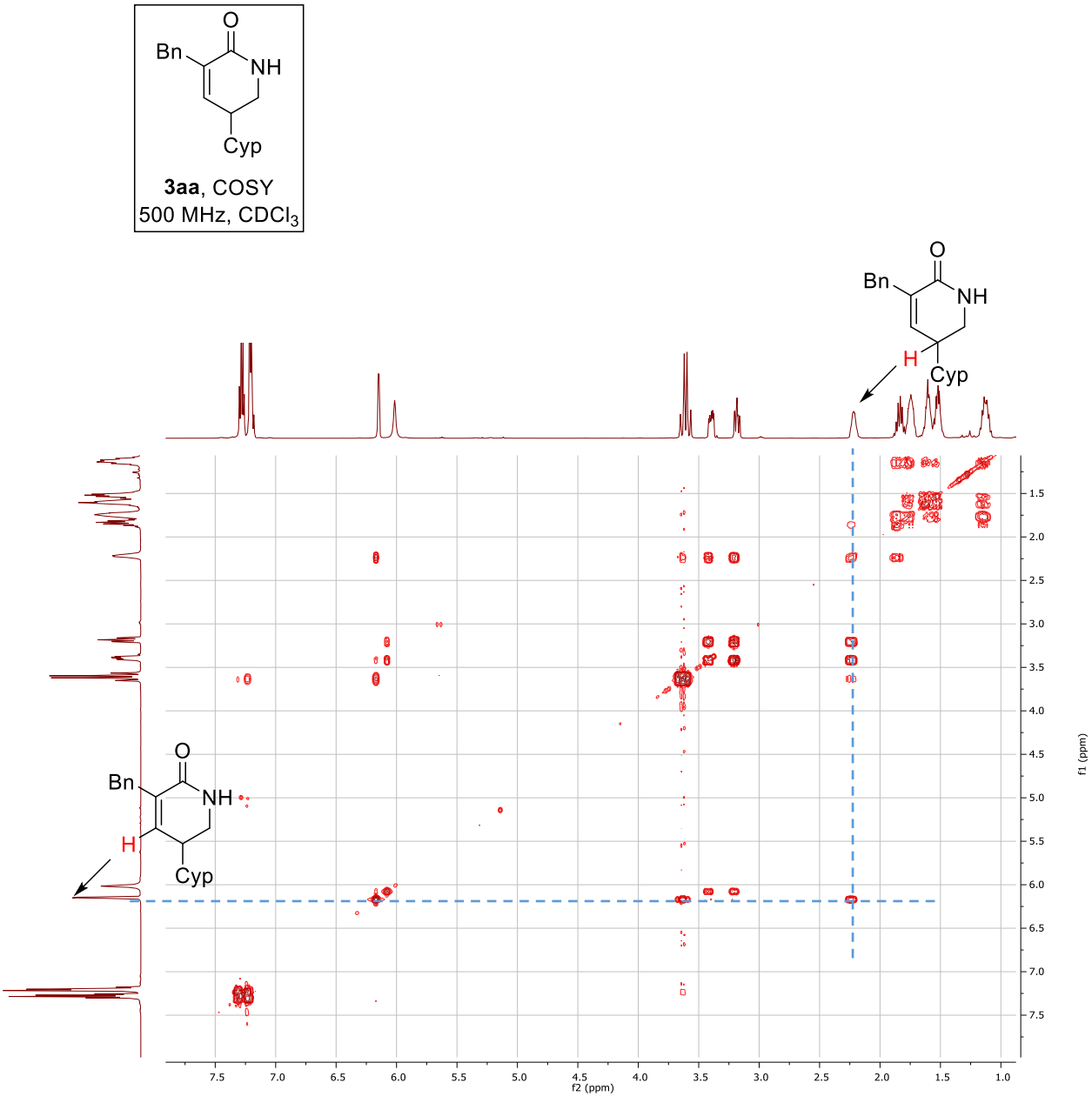

176.13
158.85
129.75
118.19
77.16 CDCl3
38.59
27.11
Br
O
N
H
OPiv
1h, 13C NMR
126 MHz, CDCl3
f1 (ppm)

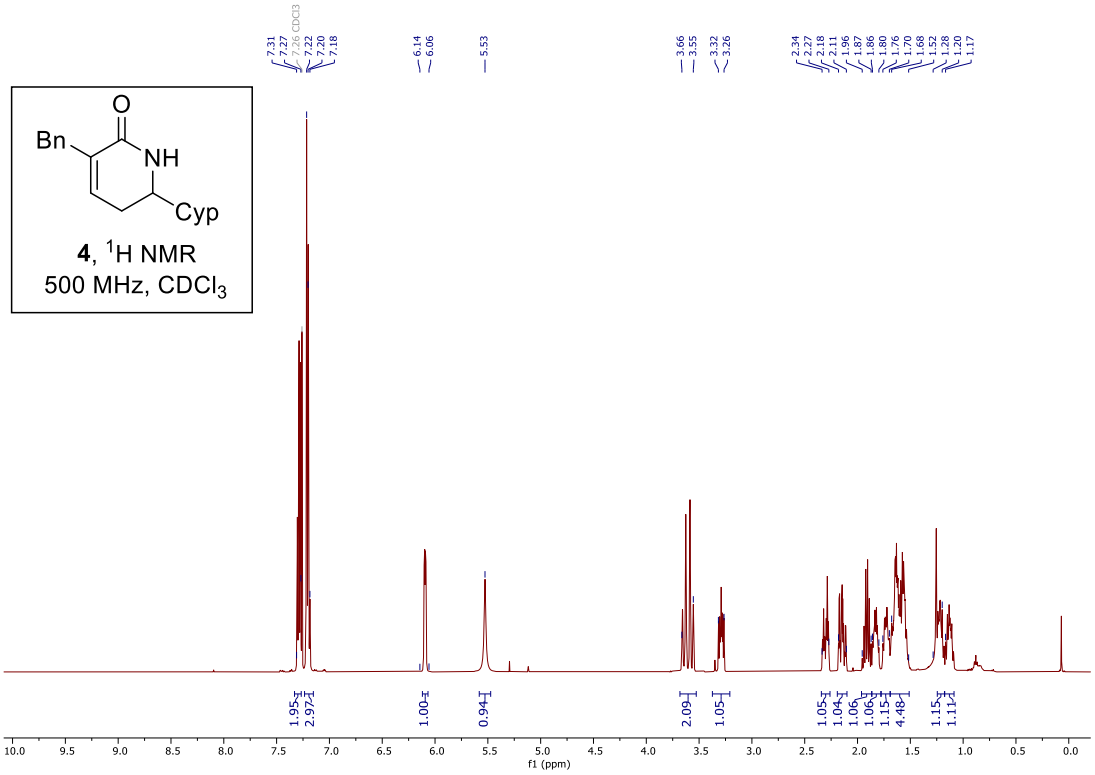

9.10
7.26 CDCl3
5.93
5.89
5.88
5.87
5.87
5.86
5.85
5.84
5.83
5.83
5.81
5.50
5.22
5.15
3.10
3.09
1.33
O
N
H
OPiv
1i, 1H NMR
500 MHz, CDCl3
0.97
1.01
0.96
1.00
1.99
2.05
9.01
f1 (ppm)

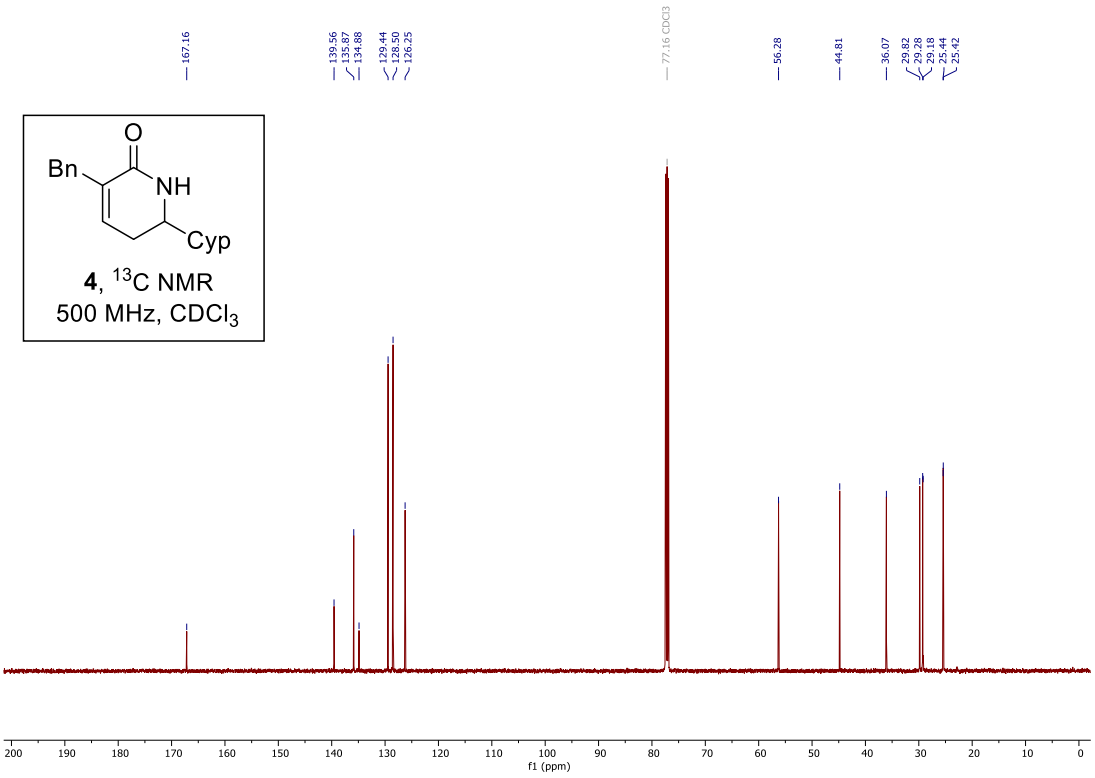

177.00
167.02
139.76
134.60
122.49
118.08
77.16 CDCl3
38.54
36.32
27.13
O
N
H
OPiv
1i, 13C NMR
126 MHz, CDCl3
f1 (ppm)

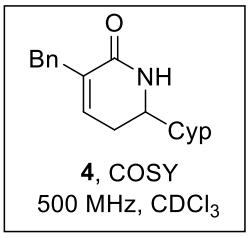

7.30
7.26 CDCl3
7.26
7.22
7.18
6.15
6.14
6.02
3.65
3.62
3.60
3.57
3.43
3.37
3.22
3.15
2.26
2.16
1.88
1.79
1.79
1.70
1.67
1.57
1.55
1.46
1.19
1.07
O
Bn
NH
Cyp
3aa, 1H NMR
500 MHz, CDCl3
2.05
3.03
1.00
0.95
1.04
1.05
1.00
1.00
1.07
1.38
2.08
2.09
2.10
2.12
f1 (ppm)

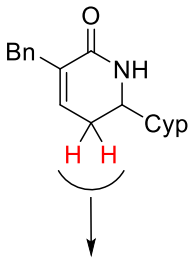

166.97
140.82
139.63
134.21
129.28
128.46
126.19
77.16 CDCl3
44.38
42.07
40.14
36.35
31.00
30.31
25.35
25.20
O
Bn
NH
Cyp
3aa, 13C NMR
126 MHz, CDCl3
f1 (ppm)

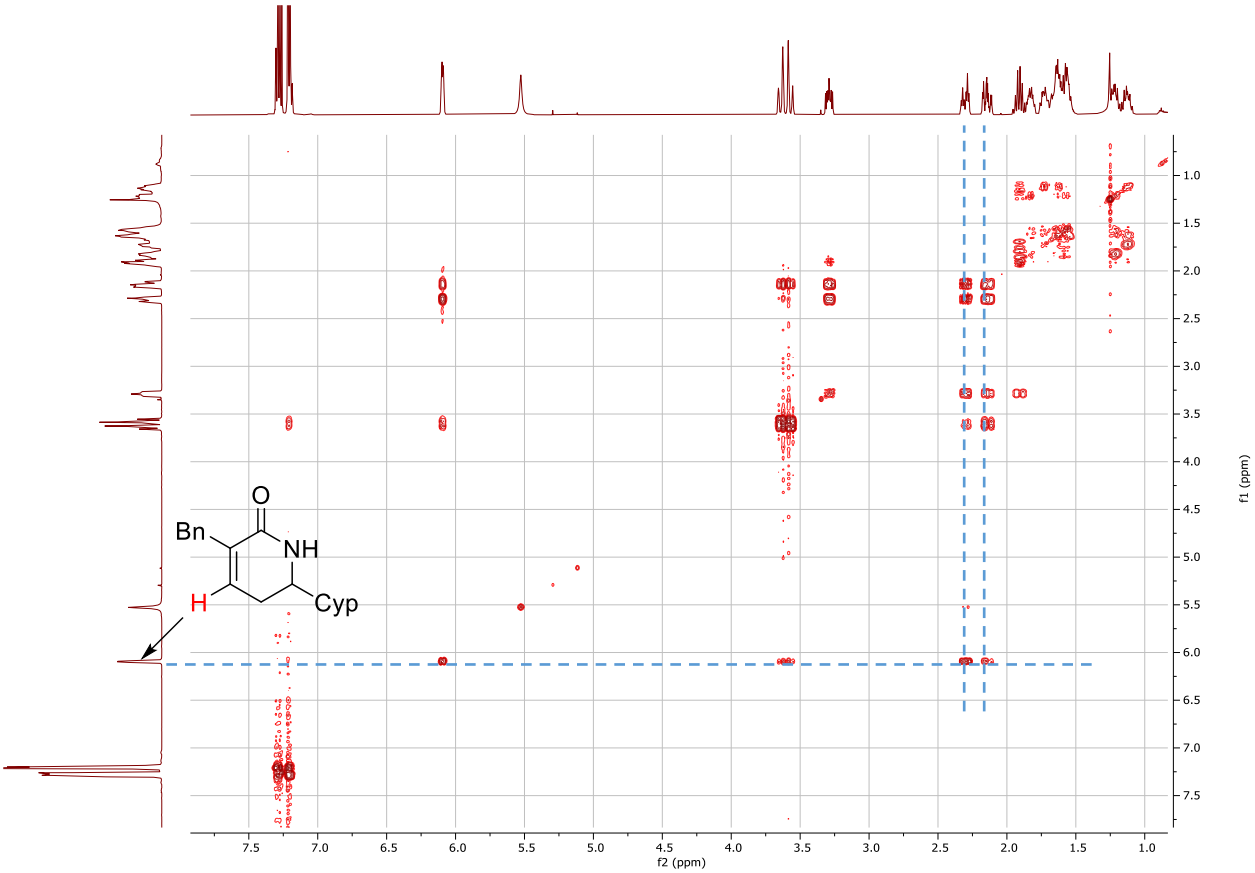

O
Bn
NH
Cyp
3aa, COSY
500 MHz, CDCl3
H
f2 (ppm)
f1 (ppm)

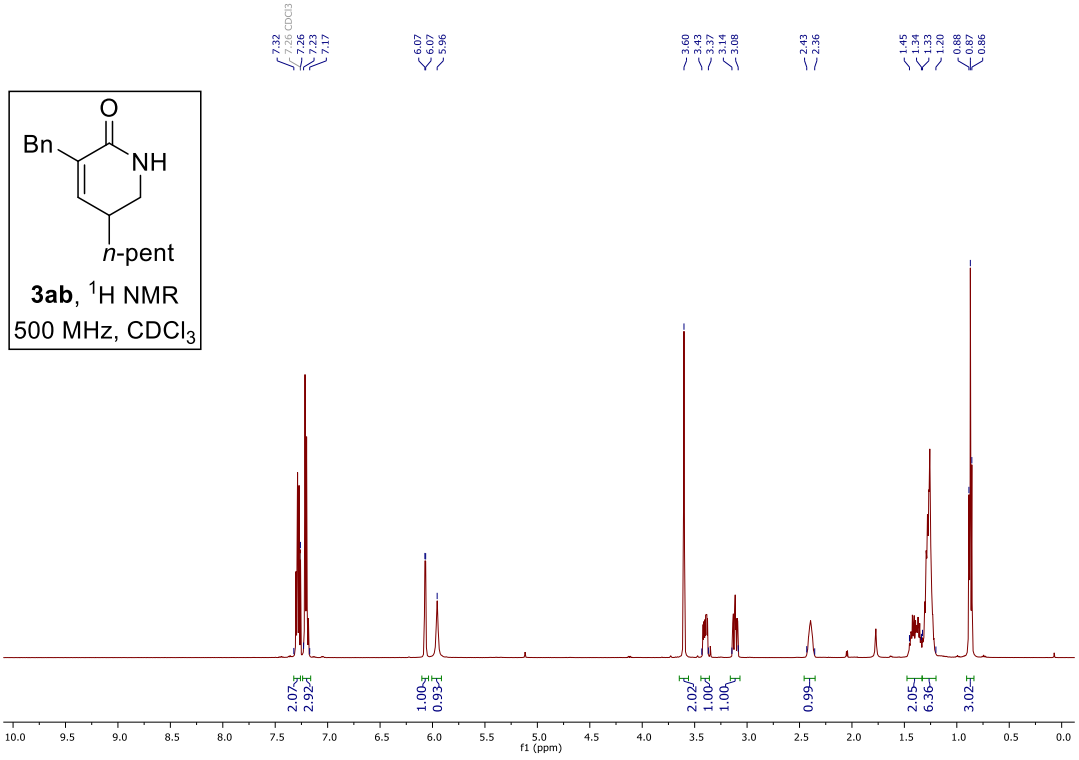

Bn
O
NH
Cyp
4, 1H NMR
500 MHz, CDCl3
7.31
7.27
7.26 CDCl3
7.22
7.20
7.18
6.14
6.06
5.53
3.66
3.55
3.32
3.26
2.34
2.27
2.18
2.11
1.96
1.87
1.86
1.80
1.76
1.70
1.68
1.52
1.28
1.20
1.17
1.95
2.97
1.00
0.94
2.09
1.05
1.05
1.04
1.06
1.06
1.15
4.48
1.15
1.14
f1 (ppm)

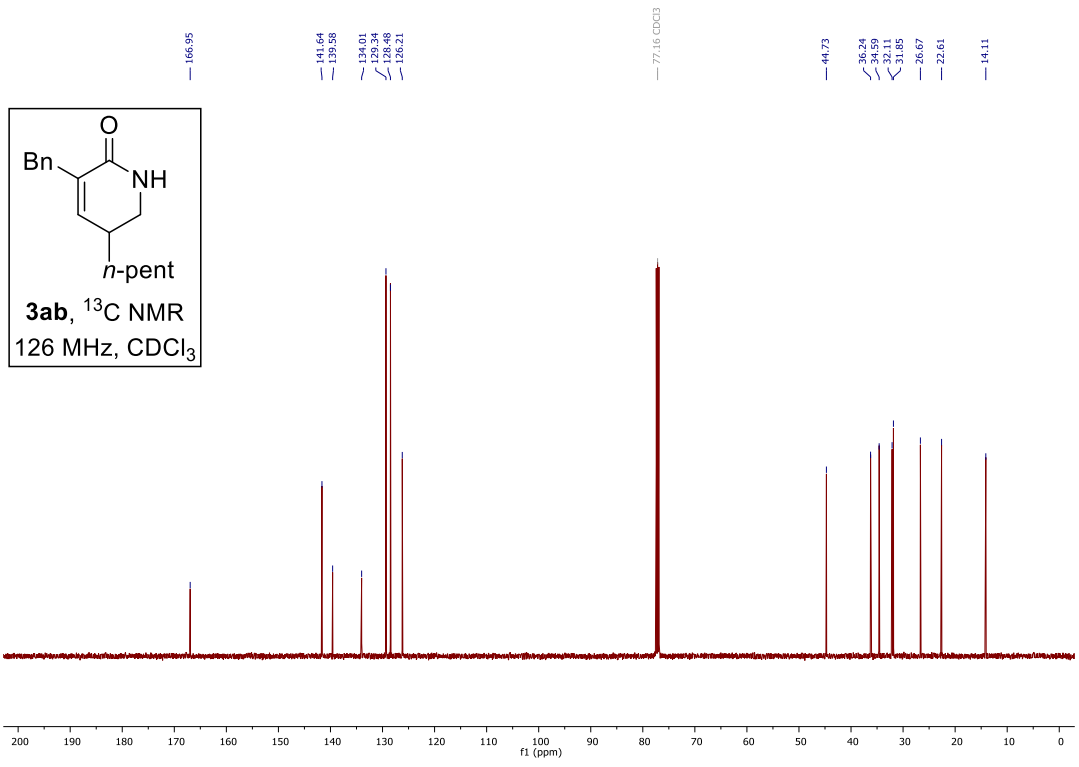

167.16
139.56
135.87
134.88
129.44
128.50
126.25
77.16 CDCl3
56.28
44.81
36.07
29.82
29.28
29.18
25.44
25.42
O
Bn
NH
Cyp
4, 13C NMR
500 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

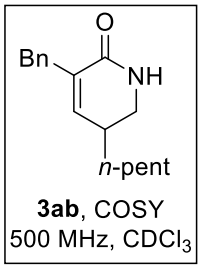

O
Bn
NH
Cyp
4, COSY
500 MHz, CDCl3


O
Bn
NH
Cyp
H H

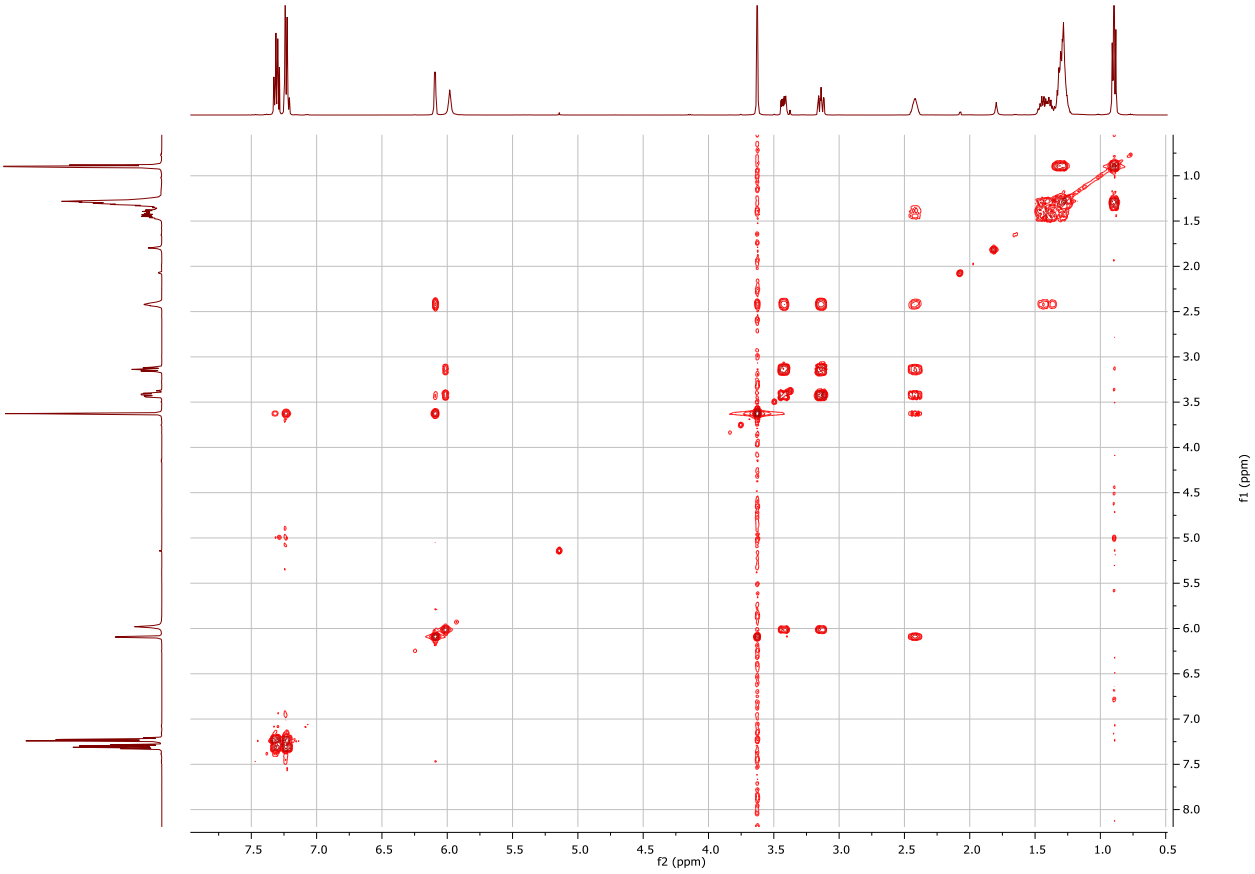

O
Bn
NH
H
Cyp
f2 (ppm)
f1 (ppm)

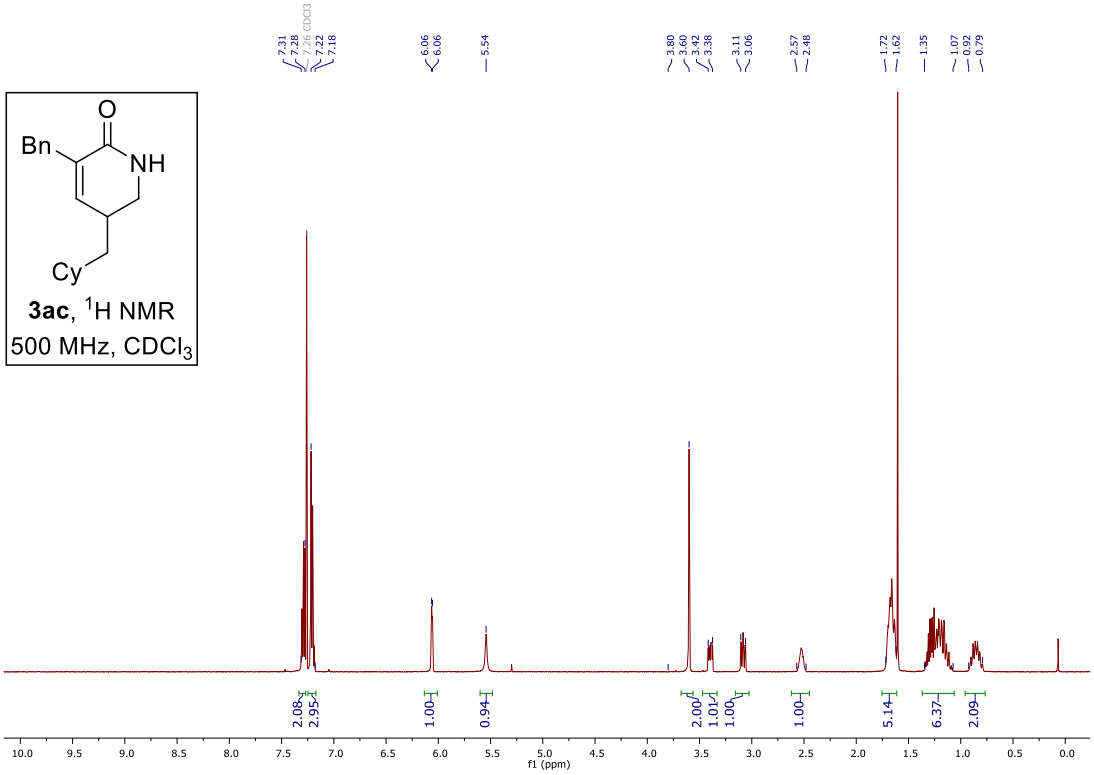

Bn
NH
O
n-pent
3ab, 1H NMR
500 MHz, CDCl3
f1 (ppm)

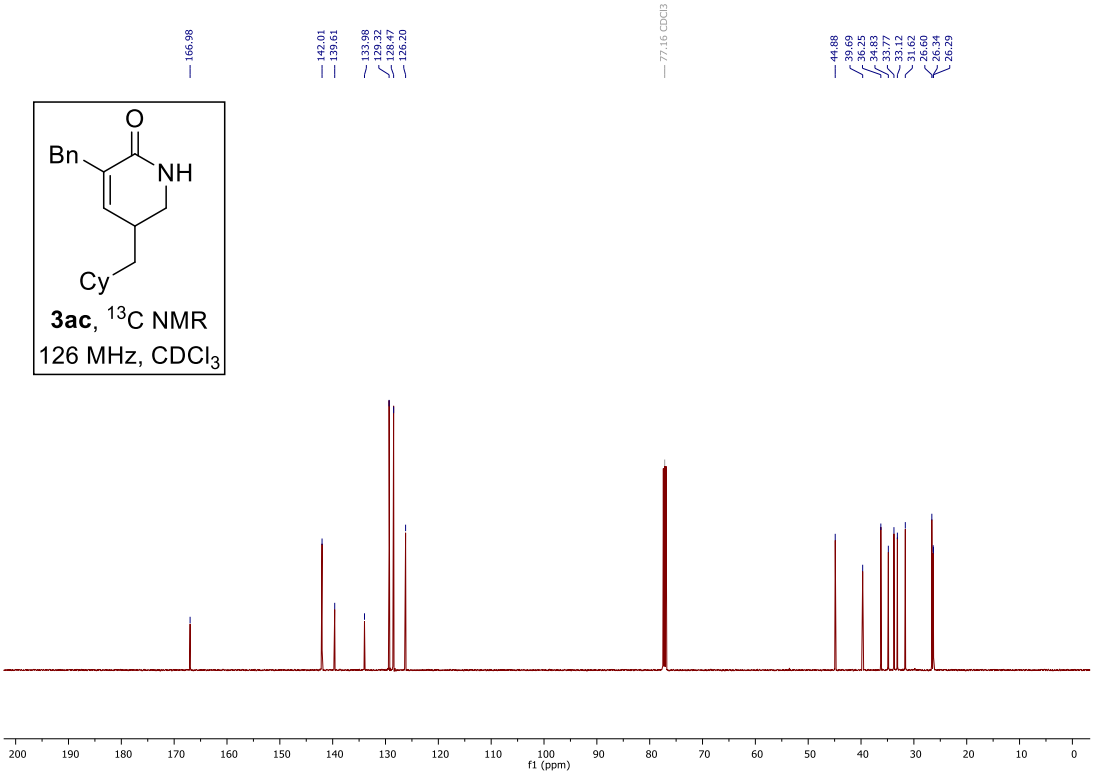

Bn
NH
O
n-pent
3ab, 13C NMR
126 MHz, CDCl3
f1 (ppm)

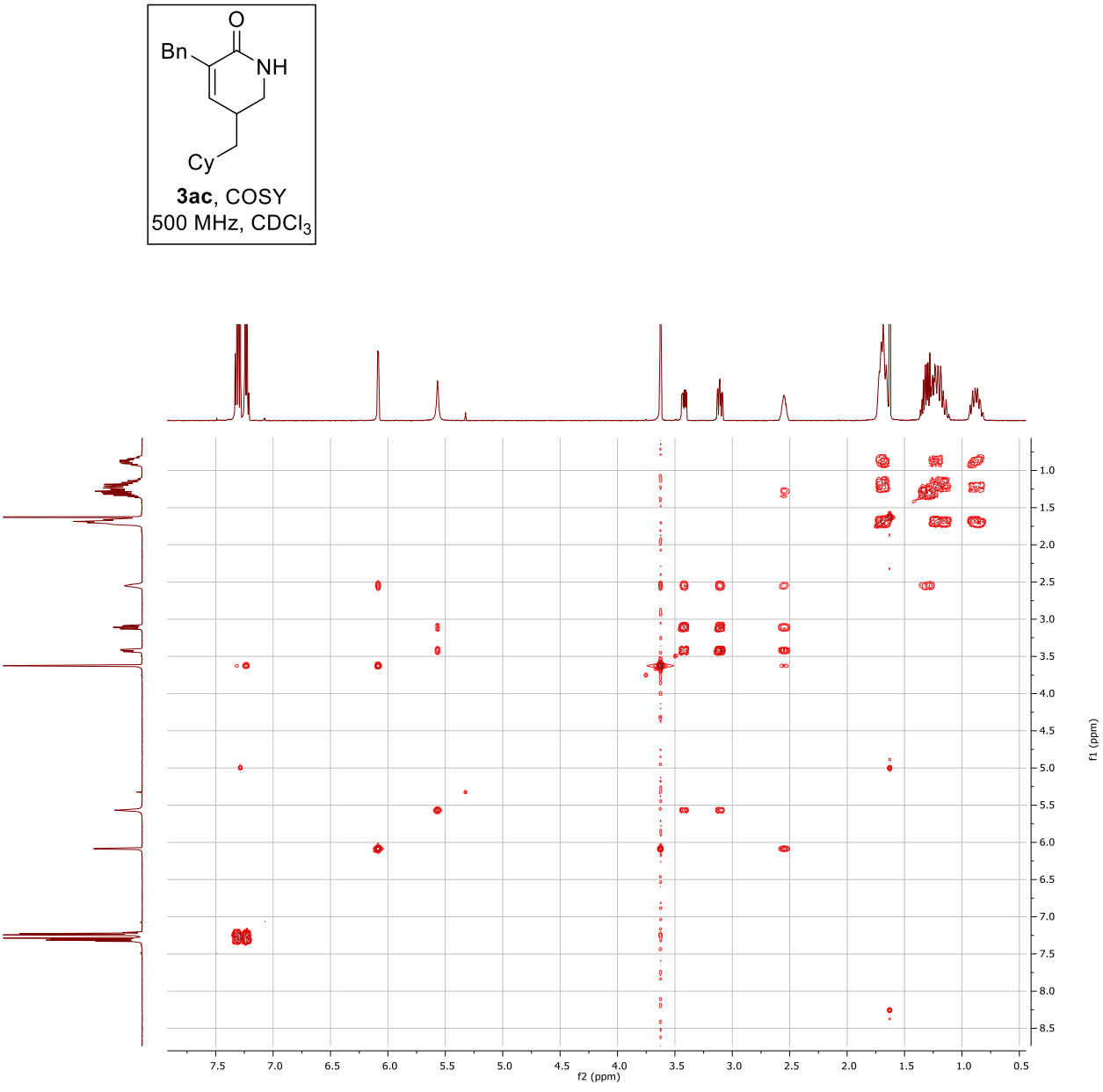


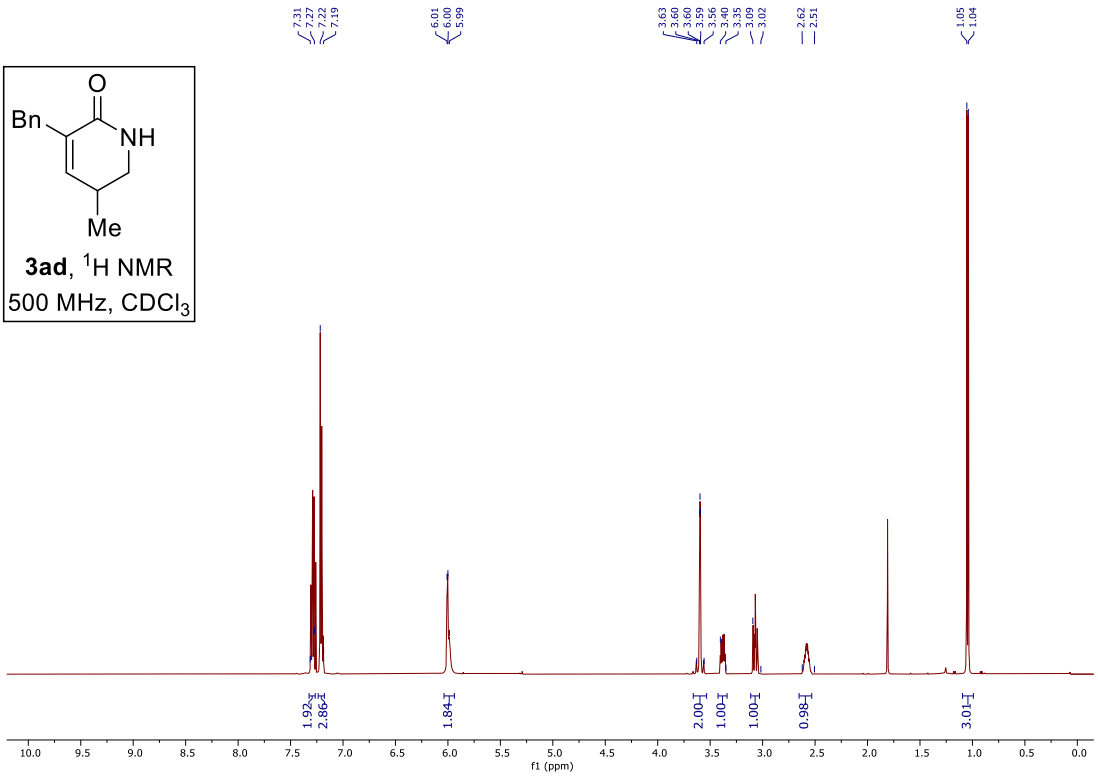
3ab, COSY
500 MHz, $CDCl_3$

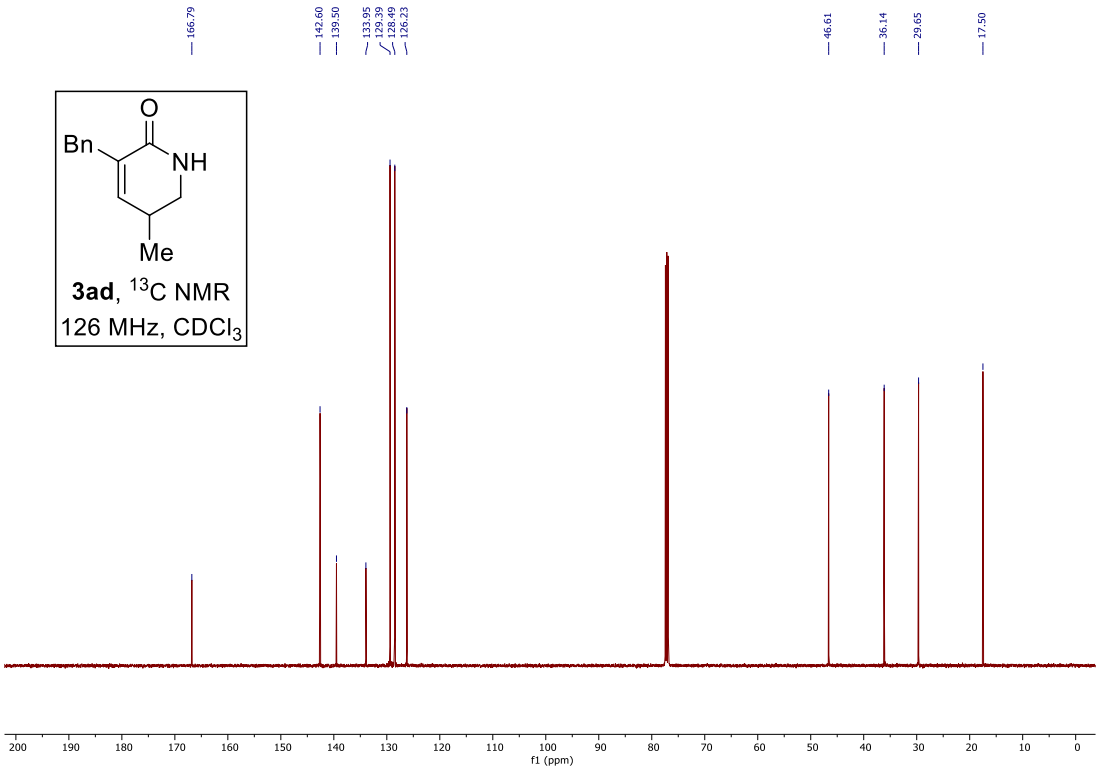


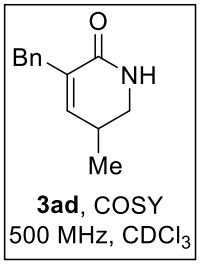

Bn
NH
O
Cy
3ac, 1H NMR
500 MHz, CDCl3
7.31
7.28
7.26 CDCl3
7.22
7.18
6.06
6.06
5.54
3.80
3.66
3.42
3.38
3.11
3.06
2.57
2.48
1.72
1.62
1.35
1.07
0.92
0.79
2.08
2.95
1.00
0.94
2.00
1.01
1.00
1.00
5.14
6.37
2.09
f1 (ppm)

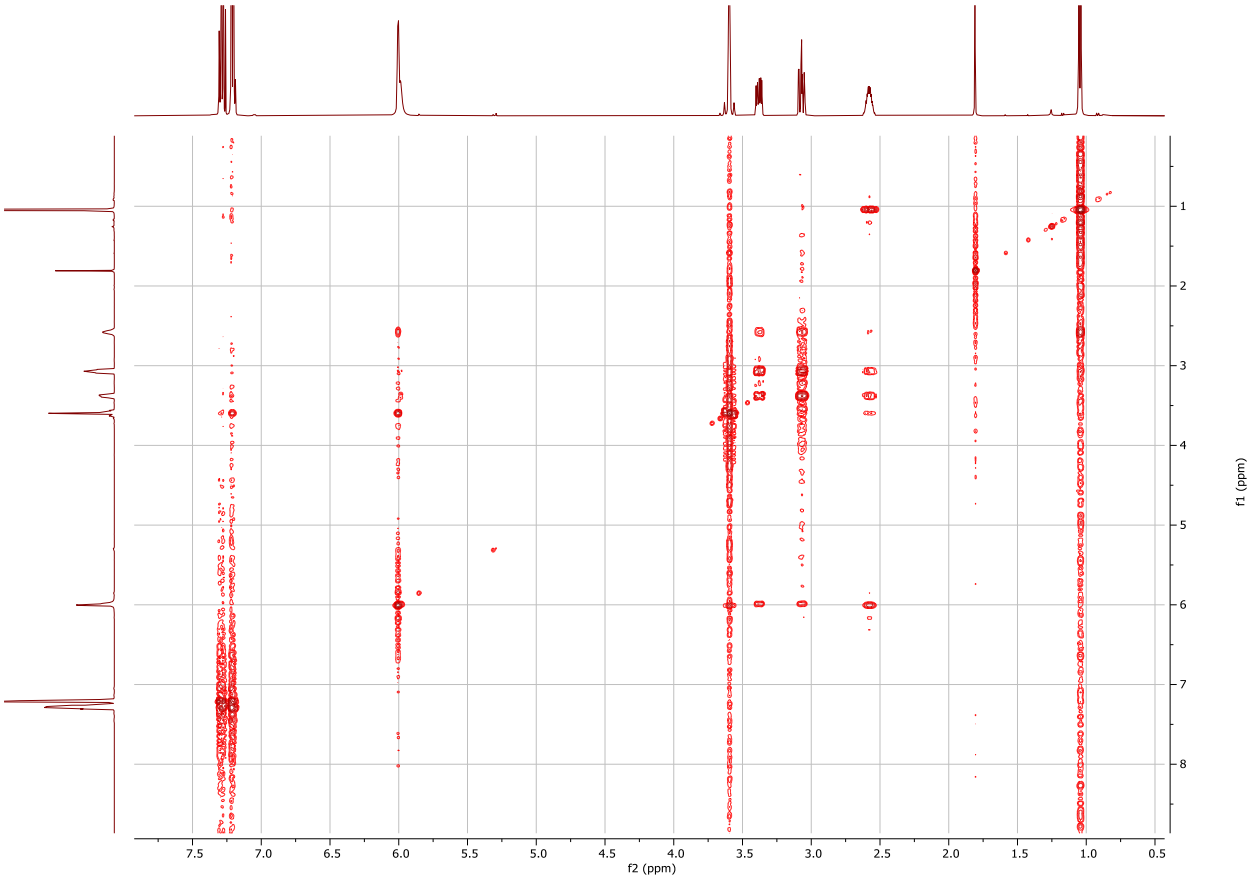

Bn
NH
O
Cy
3ac, 13C NMR
126 MHz, CDCl3
166.98
142.01
139.61
133.98
129.32
128.47
126.20
77.16 CDCl3
44.88
39.69
36.25
34.83
33.77
33.12
31.62
26.60
26.34
26.29
f1 (ppm)

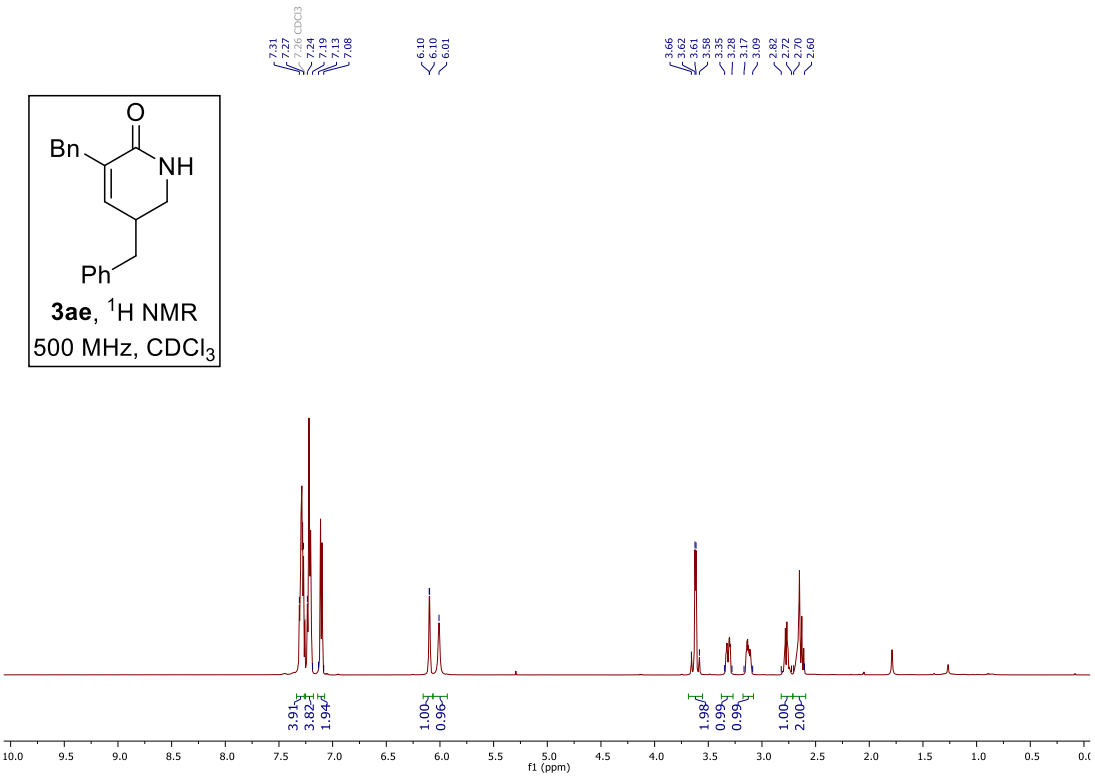

O
Bn
NH
Cy
3ac, COSY
500 MHz, CDCl3
f2 (ppm)
f1 (ppm)

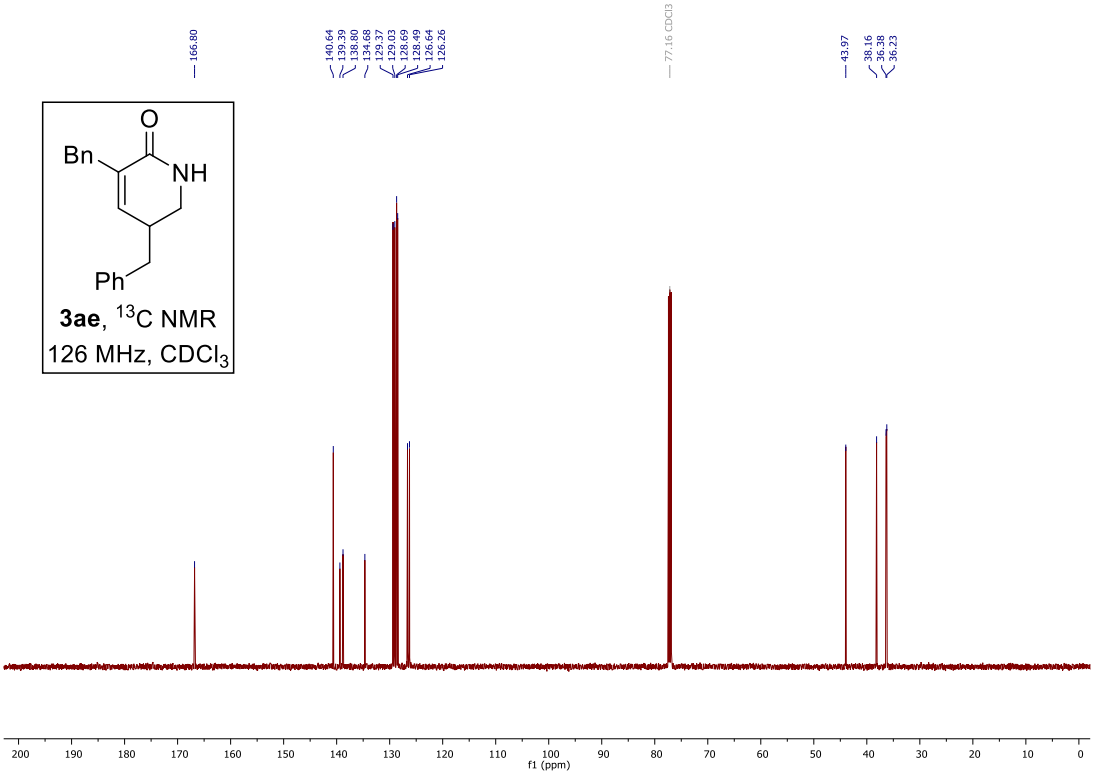

O
Bn
NH
Me
3ad, 1H NMR
500 MHz, CDCl3
7.31
7.27
7.22
7.19
6.01
6.00
5.99
3.63
3.60
3.60
3.59
3.56
3.40
3.35
3.09
3.02
2.62
2.51
1.05
1.04
1.92
2.86
1.84
2.00
1.00
1.00
0.98
3.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

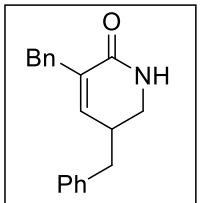

166.79
142.60
139.50
133.95
129.39
128.49
126.23
46.61
36.14
29.65
17.50
O
Bn
NH
Me
3ad, 13C NMR
126 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
Bn
NH
Me
3ad, COSY
500 MHz, CDCl3

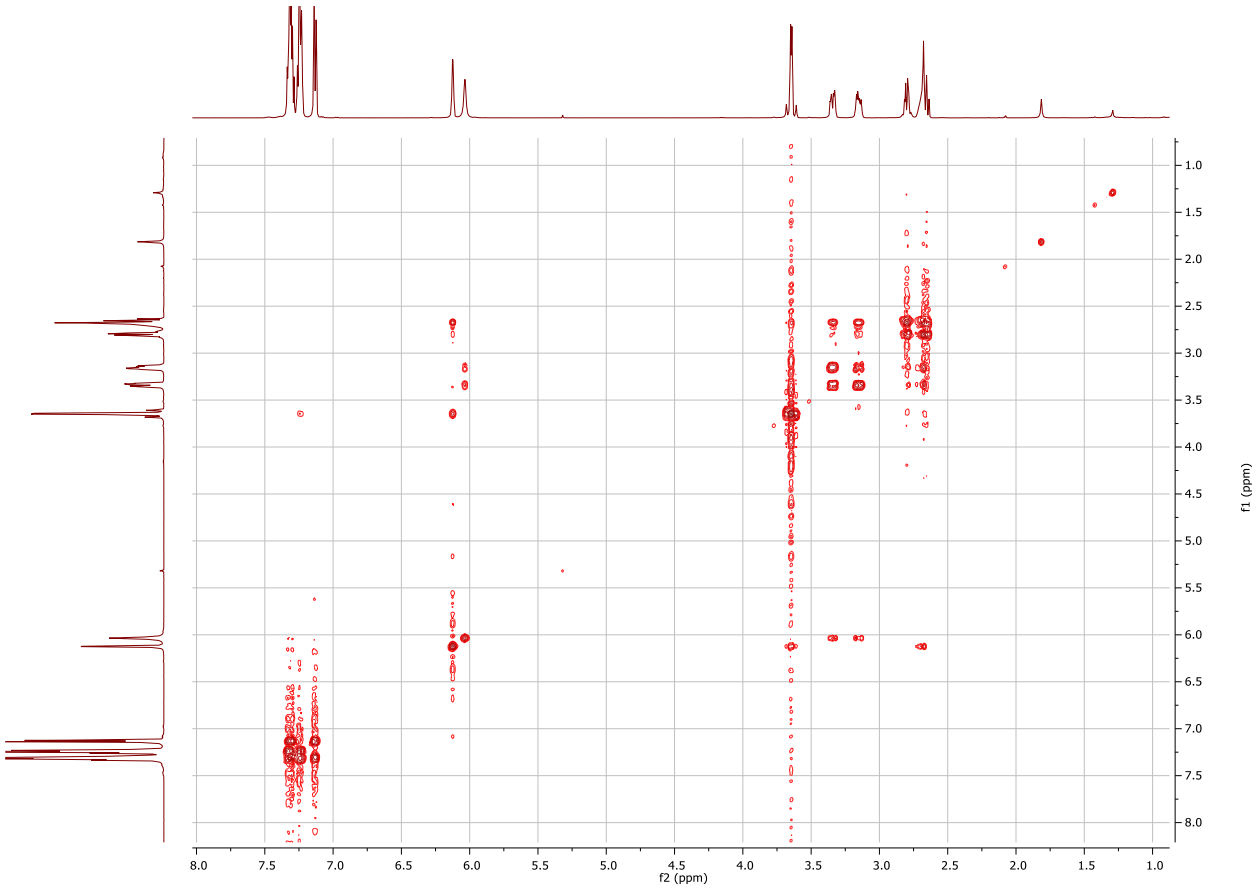

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
1
2
3
4
5
6
7
8
f1 (ppm)

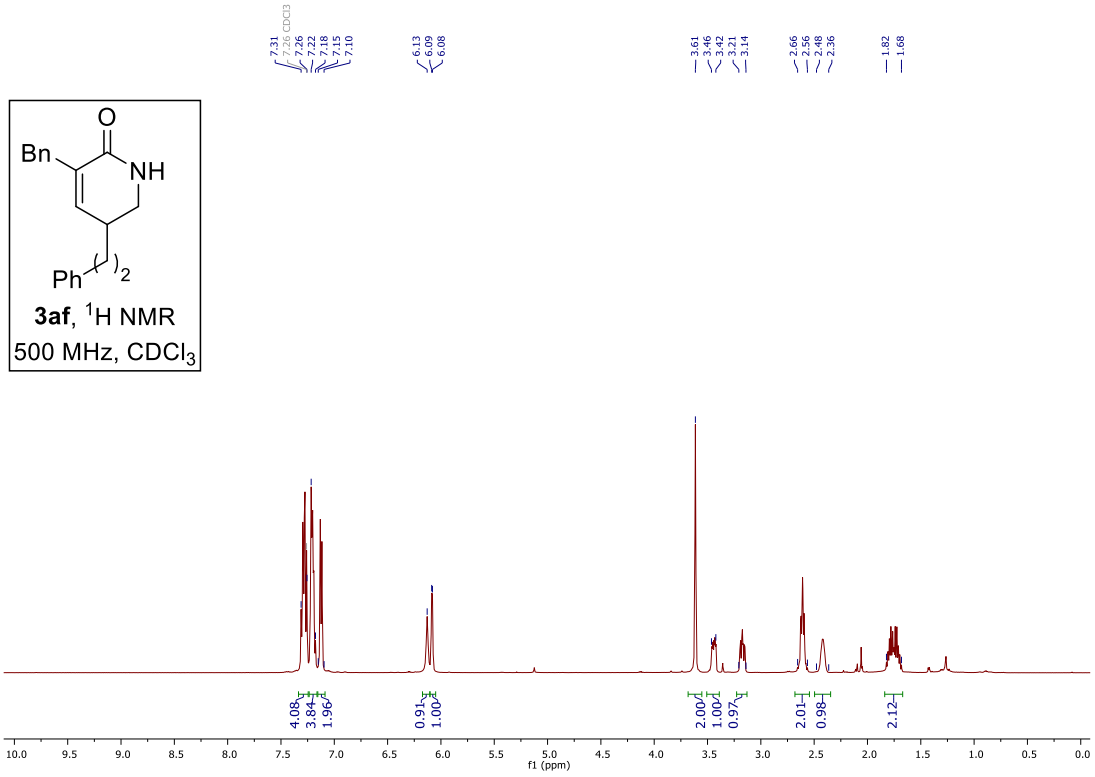

Bn
NH
O
Ph
3ae, 1H NMR
500 MHz, CDCl3
7.31
7.27
7.26 CDCl3
7.24
7.19
7.13
7.08
6.10
6.10
6.01
3.66
3.62
3.61
3.58
3.35
3.28
3.17
3.09
2.82
2.72
2.70
2.60
3.91
3.82
1.94
1.00
0.96
1.98
0.99
0.99
1.00
2.00
f1 (ppm)

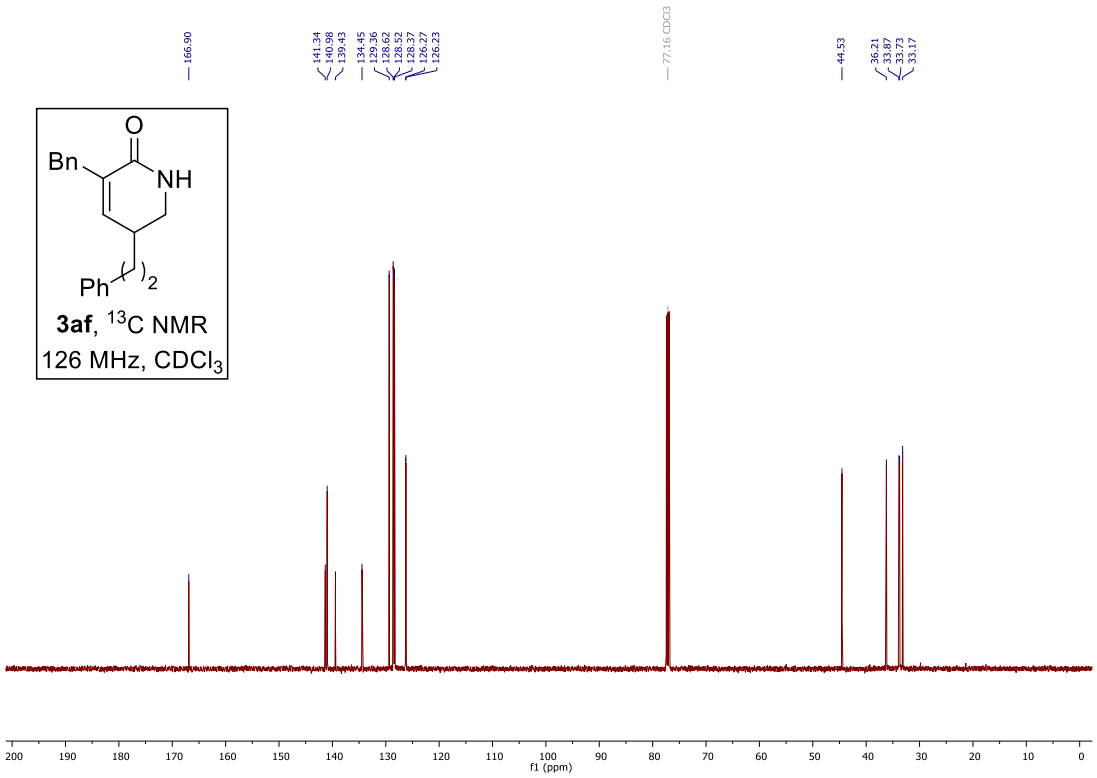

Bn
NH
O
Ph
3ae, 13C NMR
126 MHz, CDCl3
166.80
140.64
139.39
138.80
134.68
129.37
129.03
128.69
128.49
126.64
126.26
77.16 CDCl3
43.97
38.16
36.38
36.23
f1 (ppm)

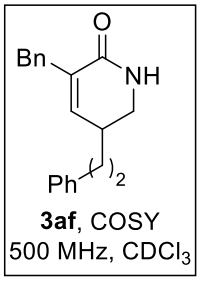


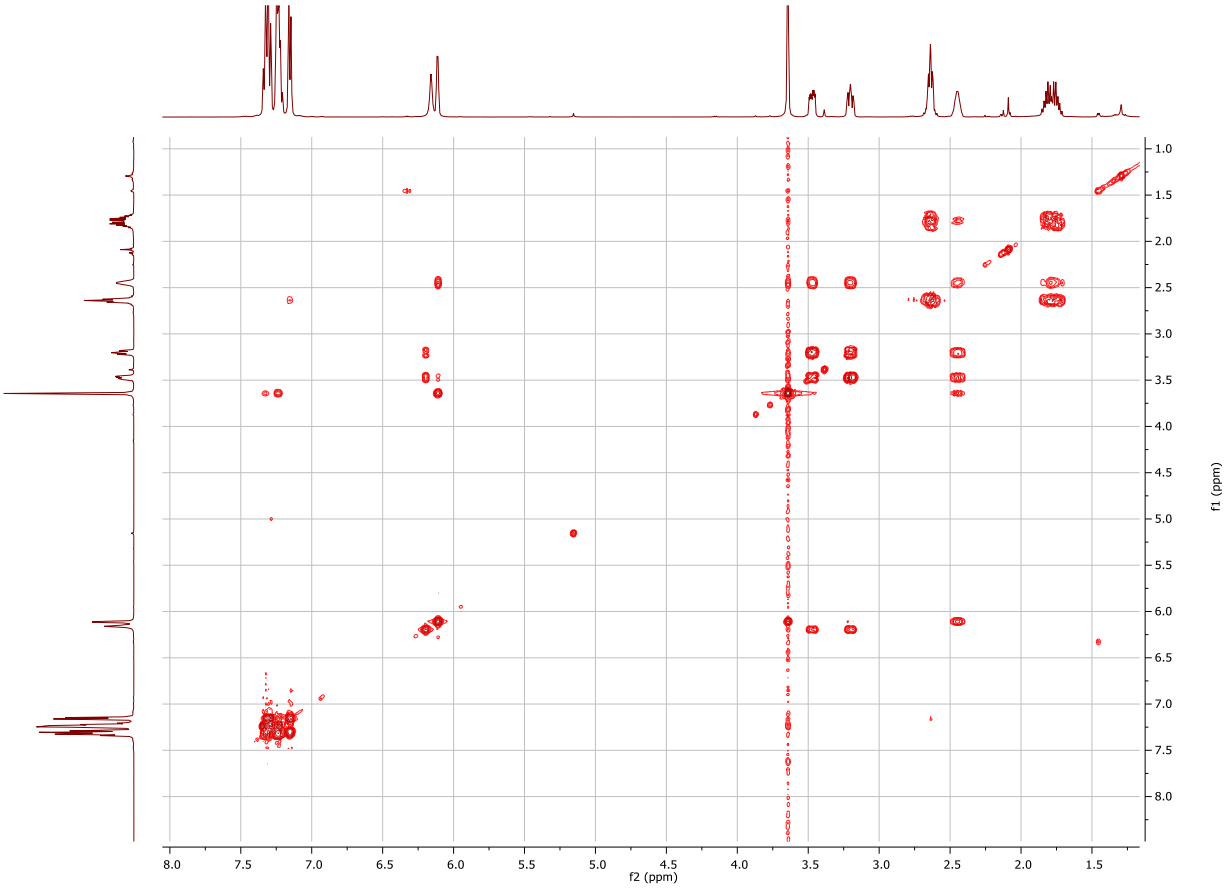
3ae, COSY
500 MHz, $CDCl_3$

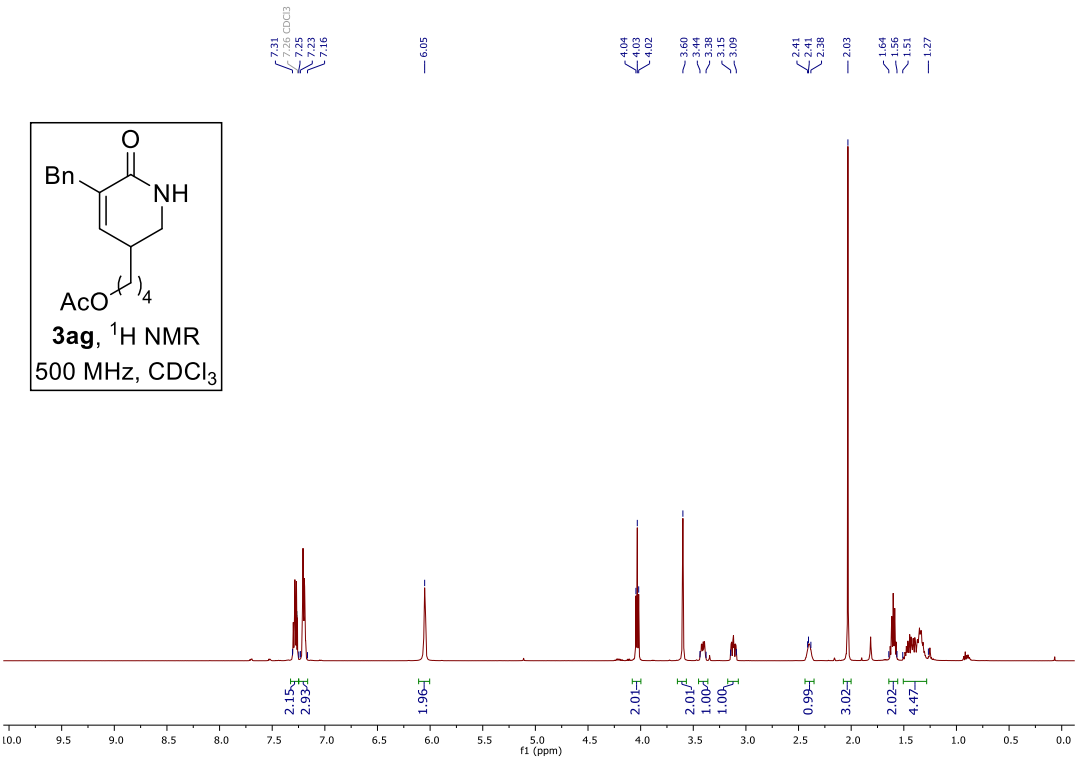


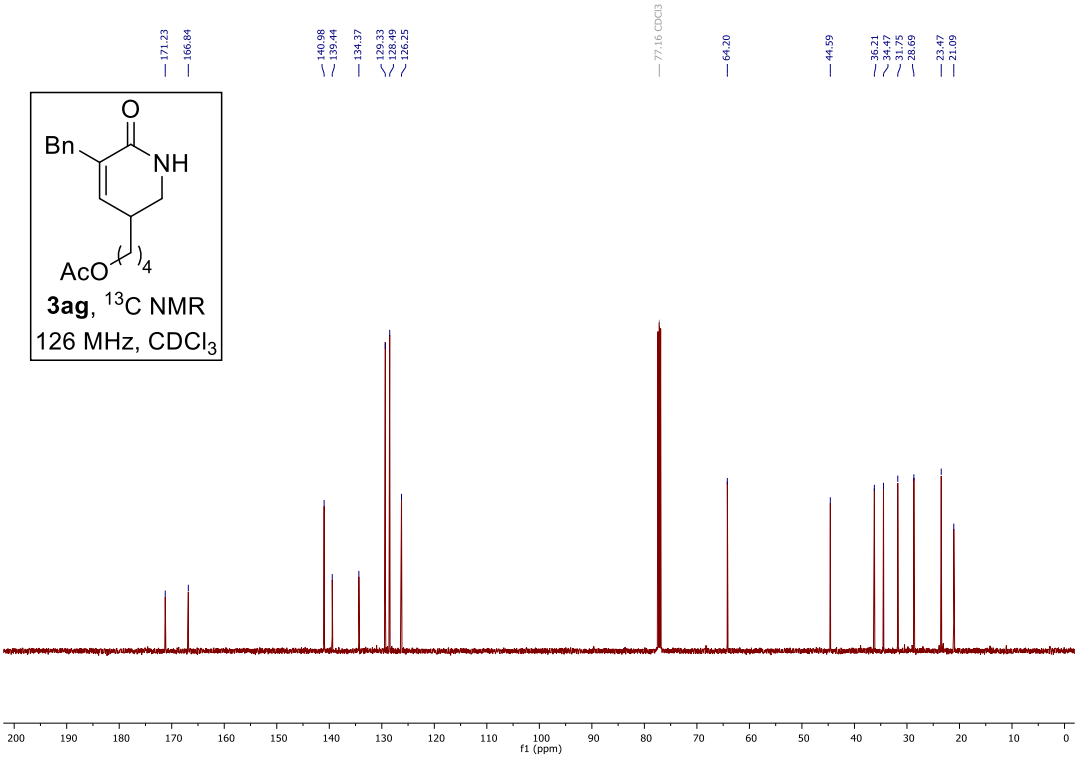

7.31
7.26 CDCl3
7.26
7.22
7.18
7.15
7.10
6.13
6.09
6.08
3.61
3.46
3.42
3.21
3.14
2.66
2.56
2.48
2.36
1.82
1.68
O
Bn
NH
Ph
2
3af, 1H NMR
500 MHz, CDCl3
4.08
3.84
1.96
0.91
1.00
2.00
1.00
0.97
2.01
0.98
2.12
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

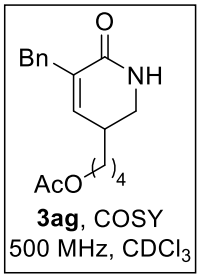

166.90
141.34
140.98
139.43
134.45
129.36
128.62
128.52
128.37
126.27
126.23
77.16 CDCl3
44.53
36.21
33.87
33.73
33.17
O
Bn
NH
Ph
2
3af, 13C NMR
126 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
Bn
NH
Ph
2
3af, COSY
500 MHz, CDCl3

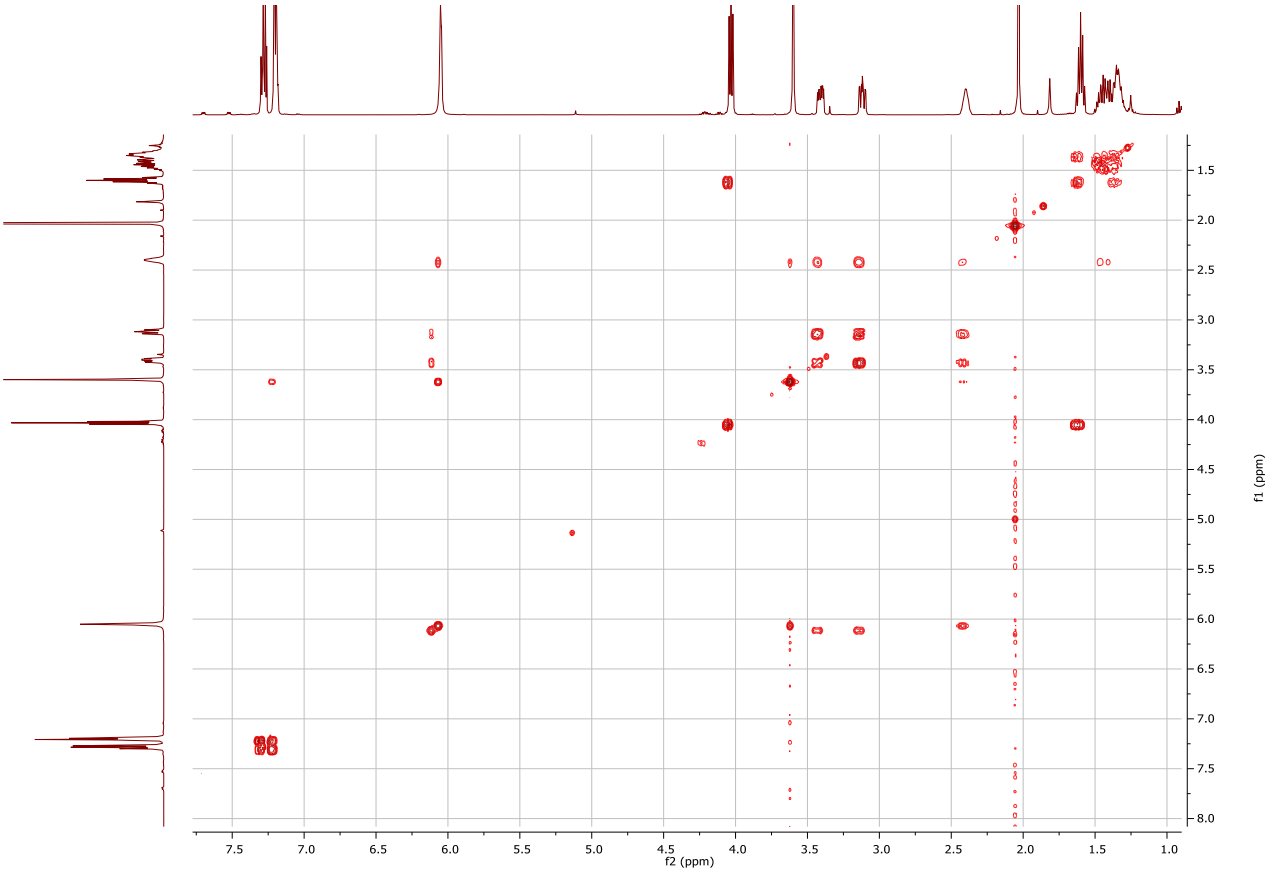

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)

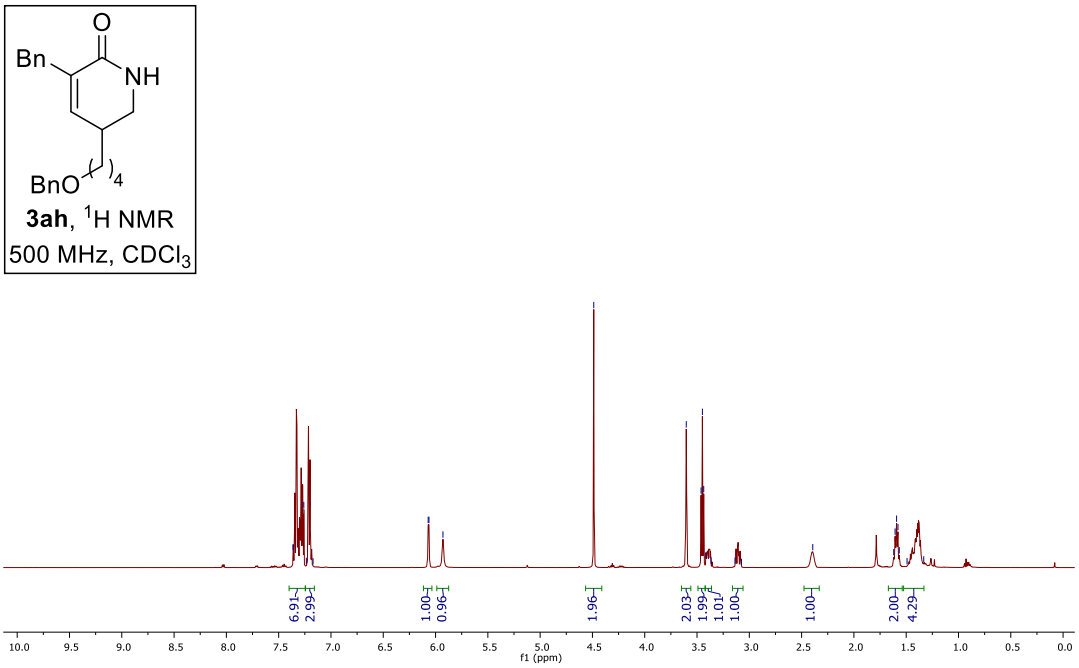

Bn
NH
O
AcO
4
3ag, 1H NMR
500 MHz, CDCl3
f1 (ppm)

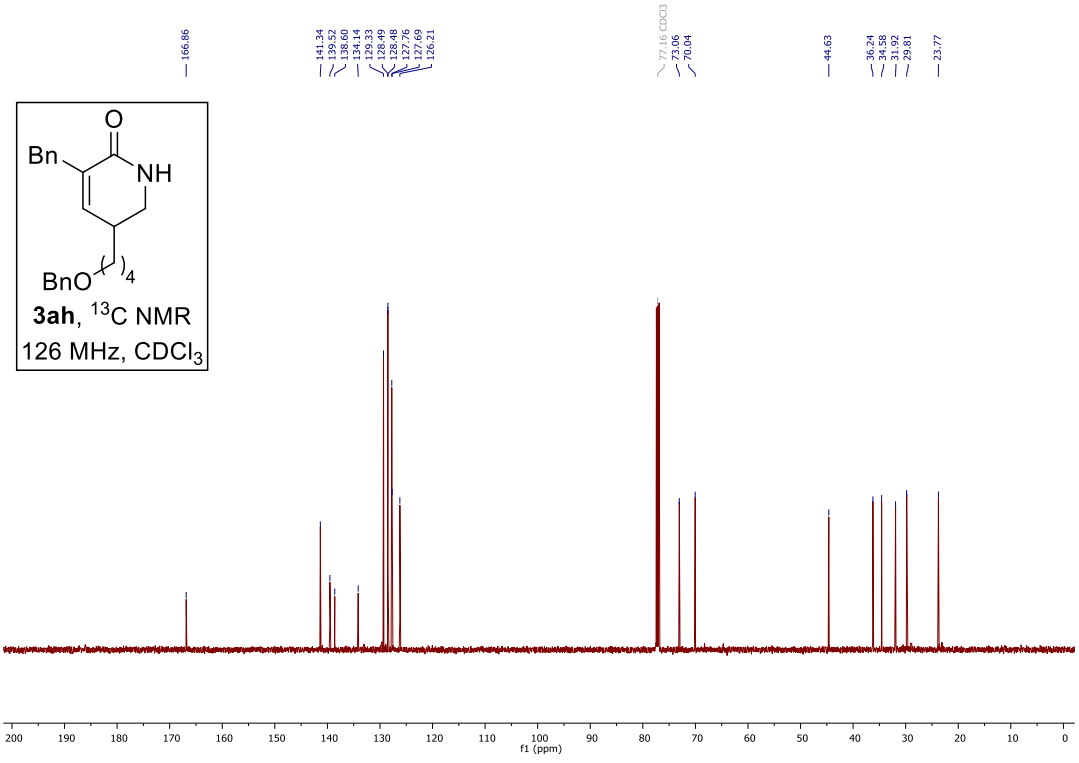

Bn
NH
O
AcO
4
3ag, 13C NMR
126 MHz, CDCl3
f1 (ppm)

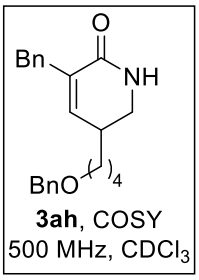


3ag, COSY
500 MHz, $CDCl_3$

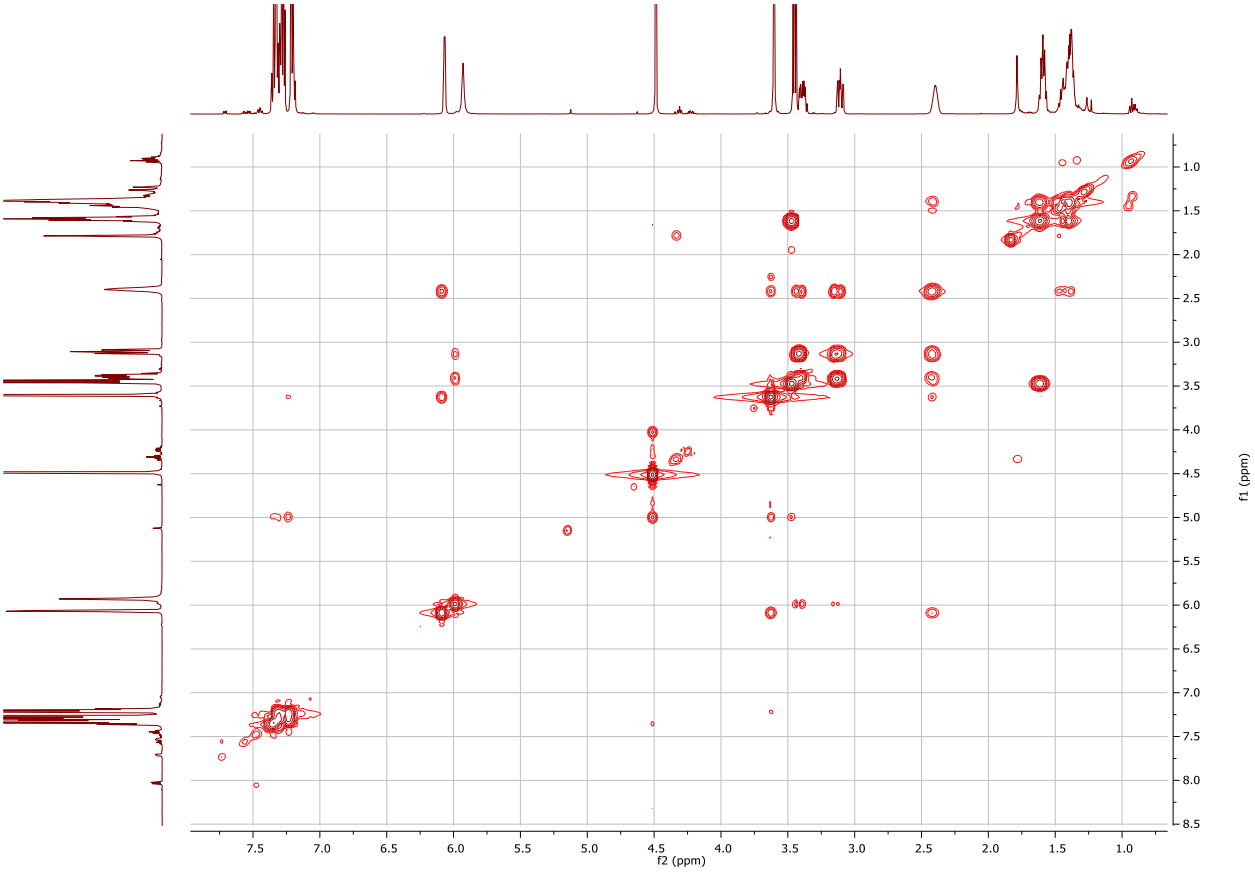


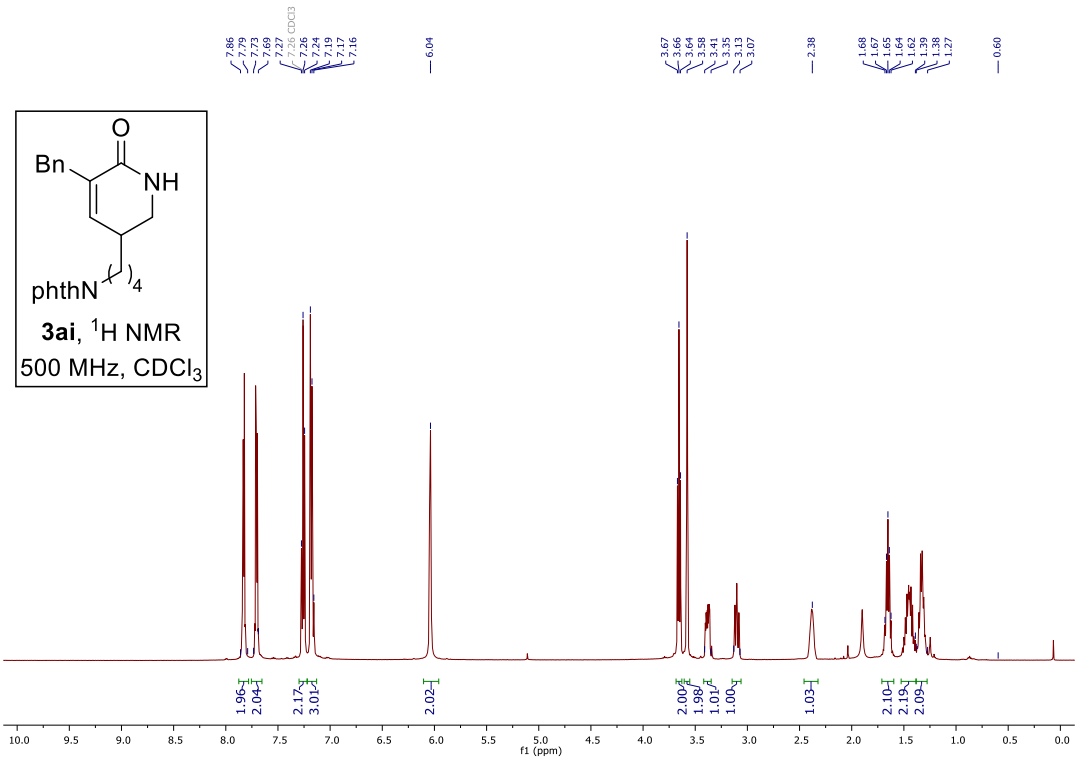

Bn
O
NH
BnO
4
3ah, 1H NMR
500 MHz, CDCl3
7.36
7.26 CDCl3
7.26
7.24
7.17
6.07
6.06
5.93
4.49
3.60
3.46
3.45
3.44
3.42
3.37
3.14
3.08
2.39
1.62
1.61
1.59
1.58
1.57
1.49
1.33
6.91
2.99
1.00
0.96
1.96
2.03
1.99
1.01
1.00
1.00
2.00
4.29
f1 (ppm)

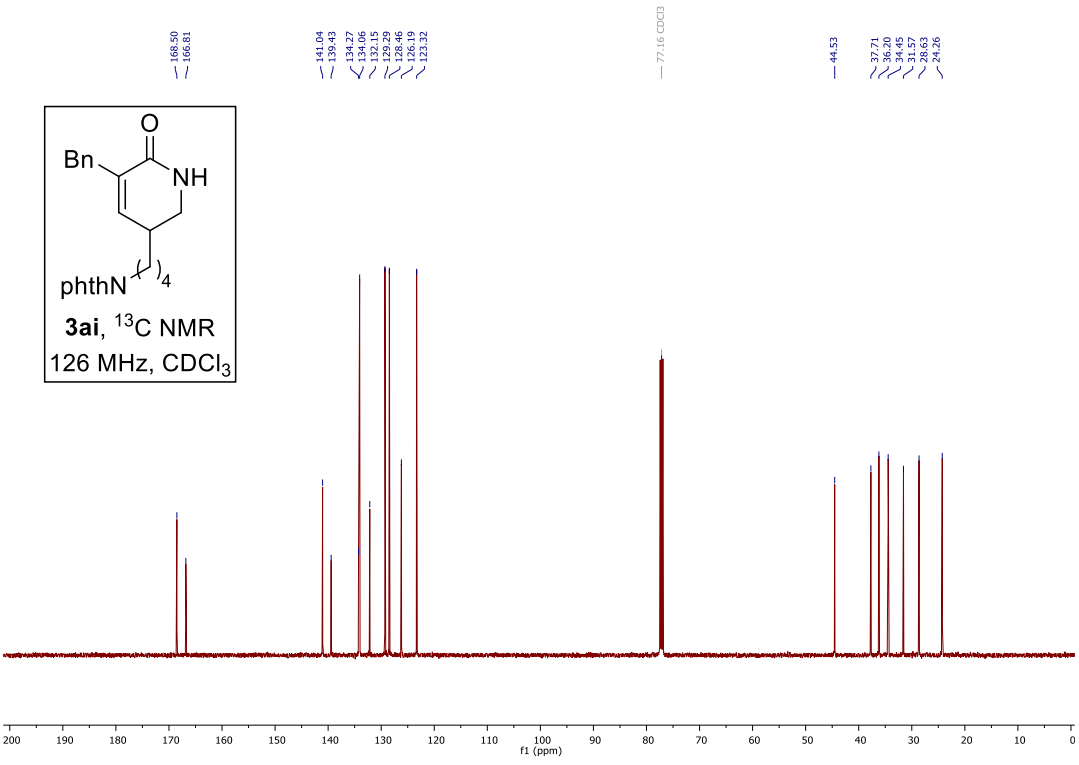

Bn
O
NH
BnO
4
3ah, 13C NMR
126 MHz, CDCl3
166.86
141.34
139.52
138.60
134.14
129.33
128.49
128.48
127.76
127.69
126.21
77.16 CDCl3
73.06
70.04
44.63
36.24
34.58
31.92
29.81
23.77
f1 (ppm)

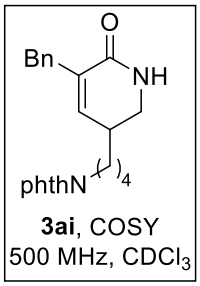


3ah, COSY
500 MHz, $CDCl_3$

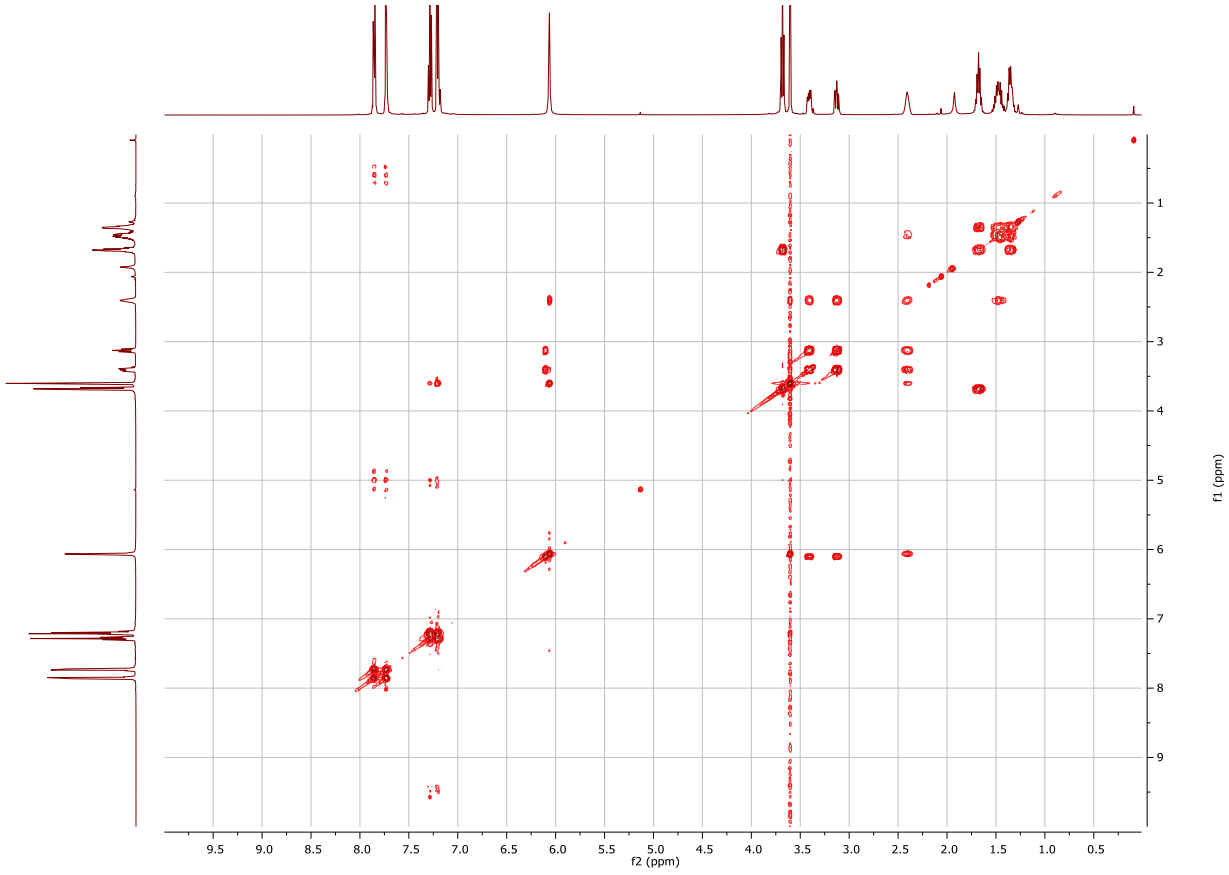


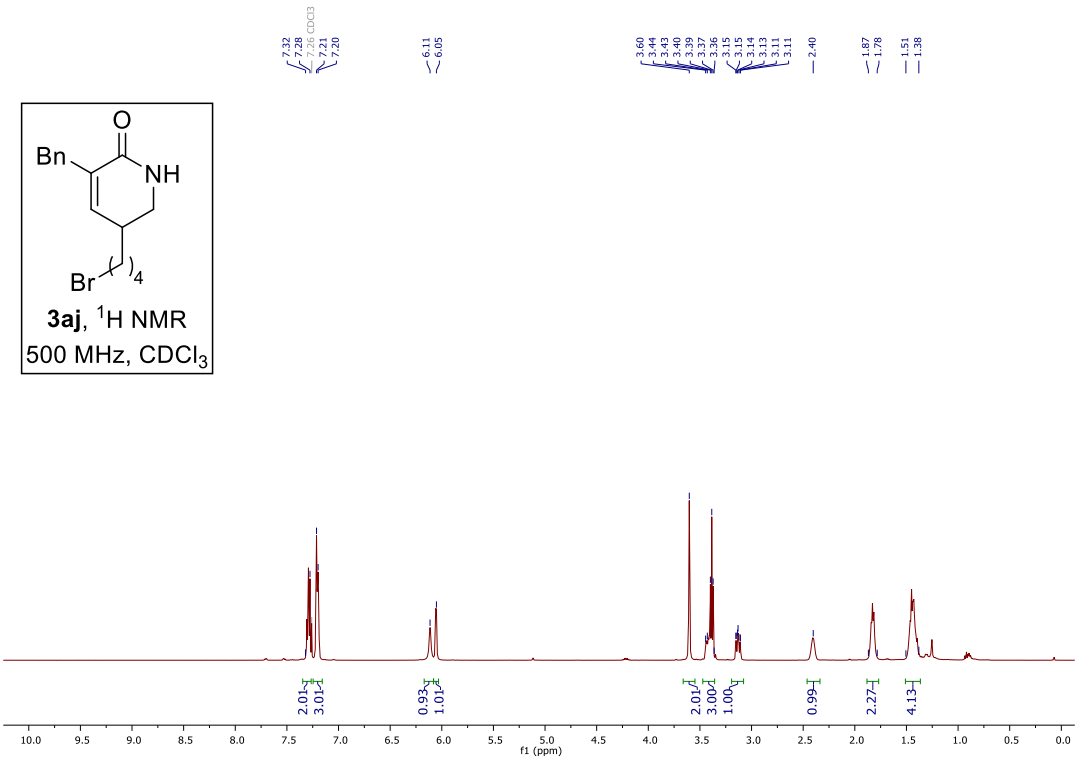

7.86
7.79
7.73
7.69
7.27
7.26 CDCl3
7.24
7.19
7.17
7.16
6.04
3.67
3.66
3.64
3.58
3.41
3.35
3.13
3.07
2.38
1.68
1.67
1.65
1.64
1.62
1.39
1.38
1.27
0.60
Bn
NH
O
phthN
4
3ai, 1H NMR
500 MHz, CDCl3
1.96
2.04
2.17
3.01
2.02
2.00
1.98
1.01
1.00
1.03
2.10
2.19
2.09
f1 (ppm)

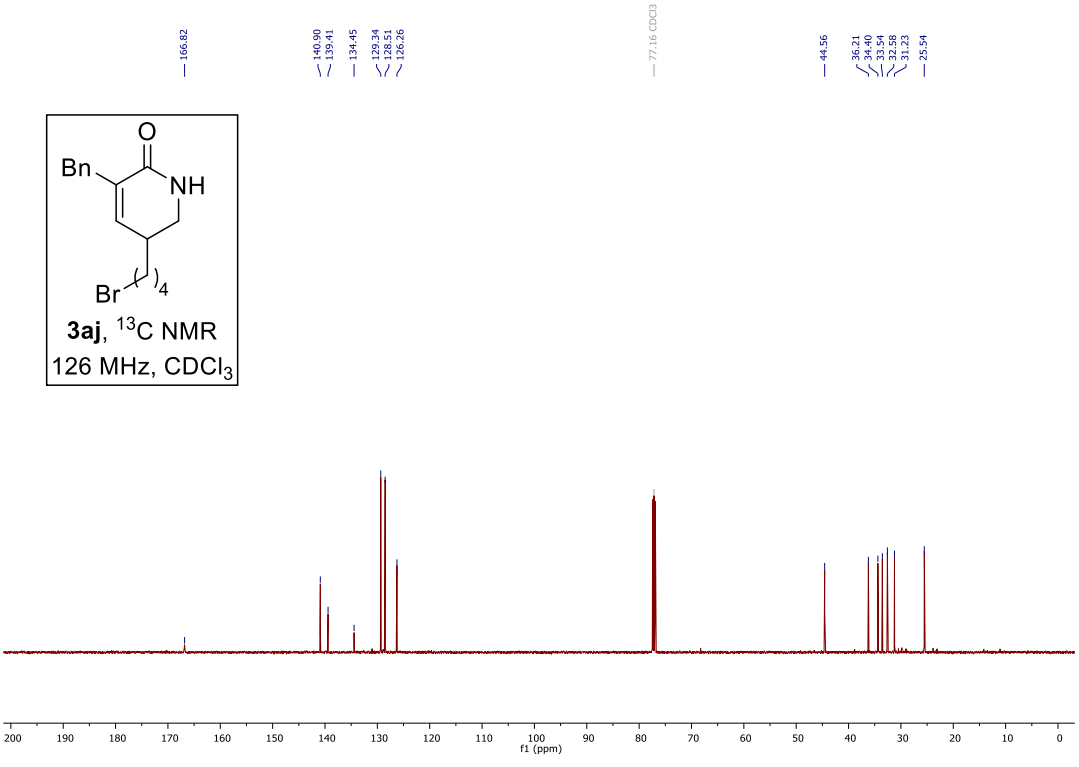

168.50
166.81
141.04
139.43
134.27
134.06
132.15
129.29
128.46
126.19
123.32
77.16 CDCl3
44.53
37.71
36.20
34.45
31.57
28.63
24.26
Bn
NH
O
phthN
4
3ai, 13C NMR
126 MHz, CDCl3
f1 (ppm)

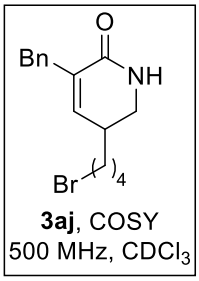


3ai, COSY
500 MHz, $CDCl_3$

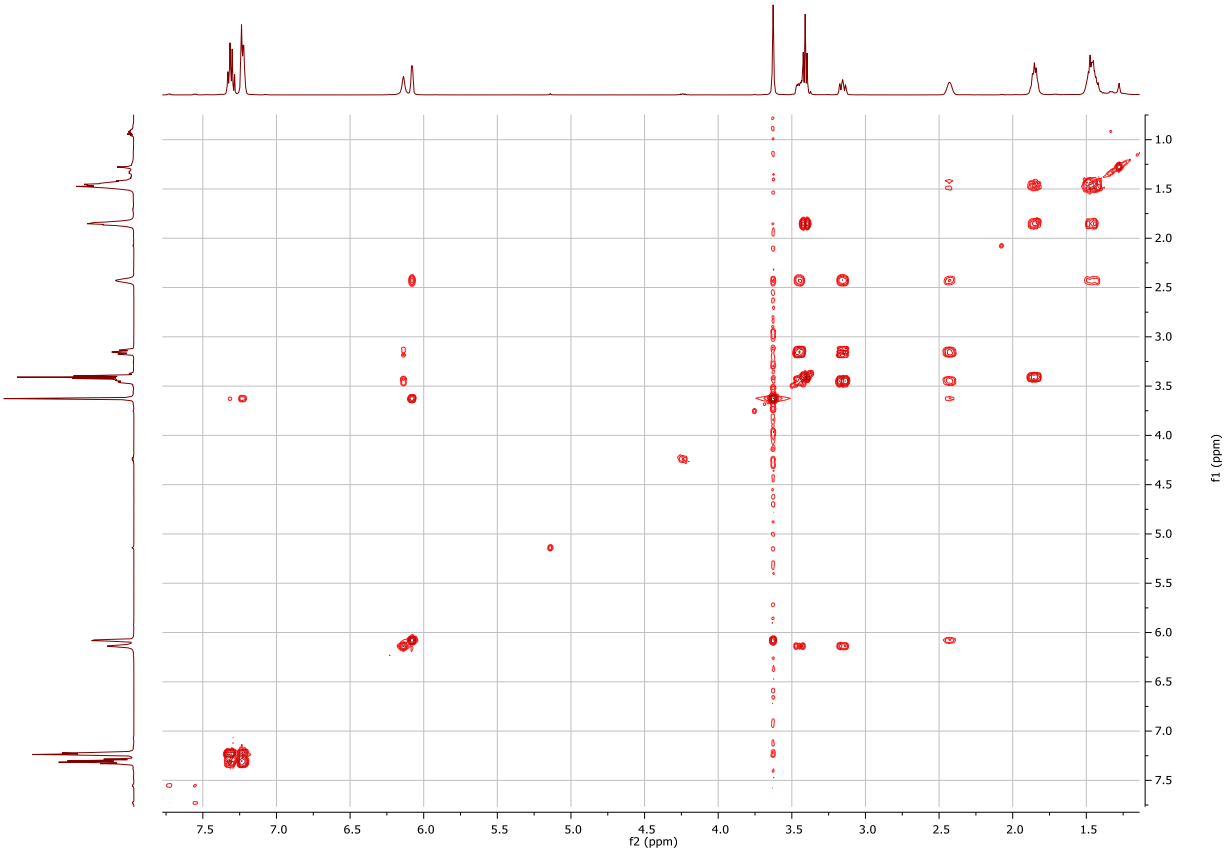


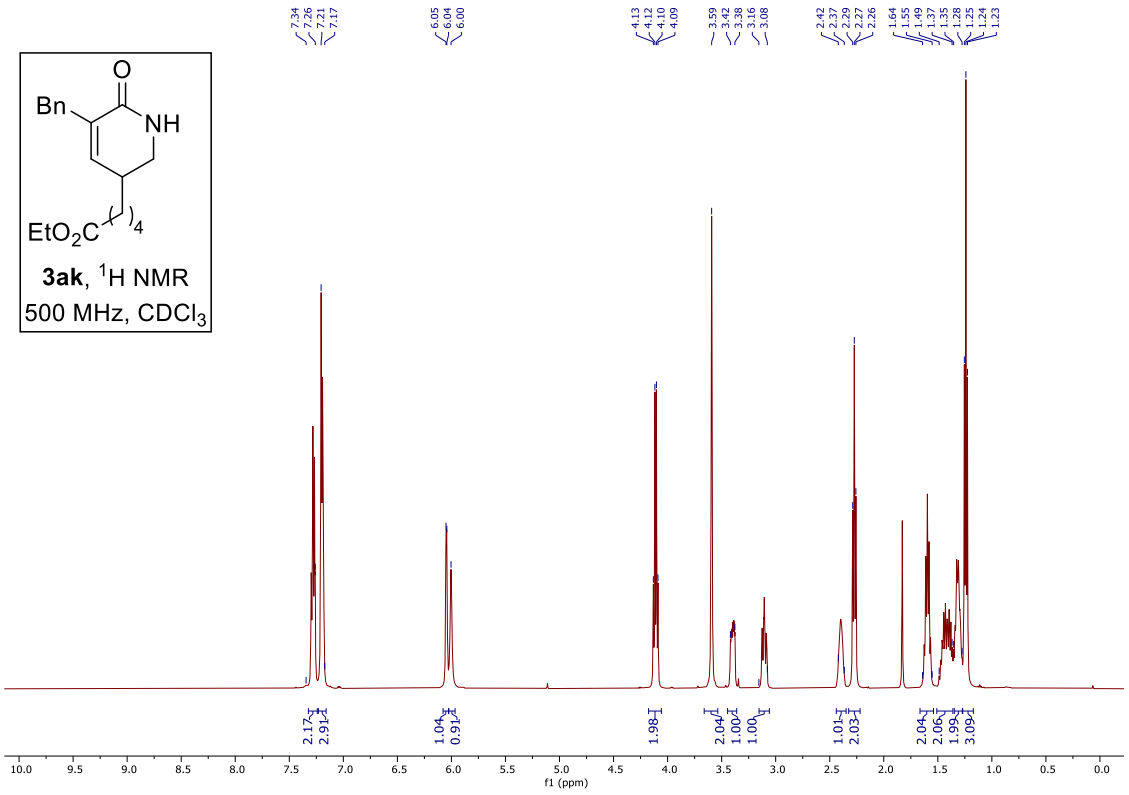

7.32
7.28
7.25
CDCl3
7.21
7.20
6.11
6.05
3.60
3.44
3.43
3.40
3.39
3.37
3.36
3.15
3.15
3.14
3.13
3.11
3.11
2.40
1.87
1.78
1.51
1.38
O
Bn
NH
Br
4
3aj, 1H NMR
500 MHz, CDCl3
2.01
3.01
0.93
1.01
2.01
3.00
1.00
0.99
2.27
4.13
f1 (ppm)

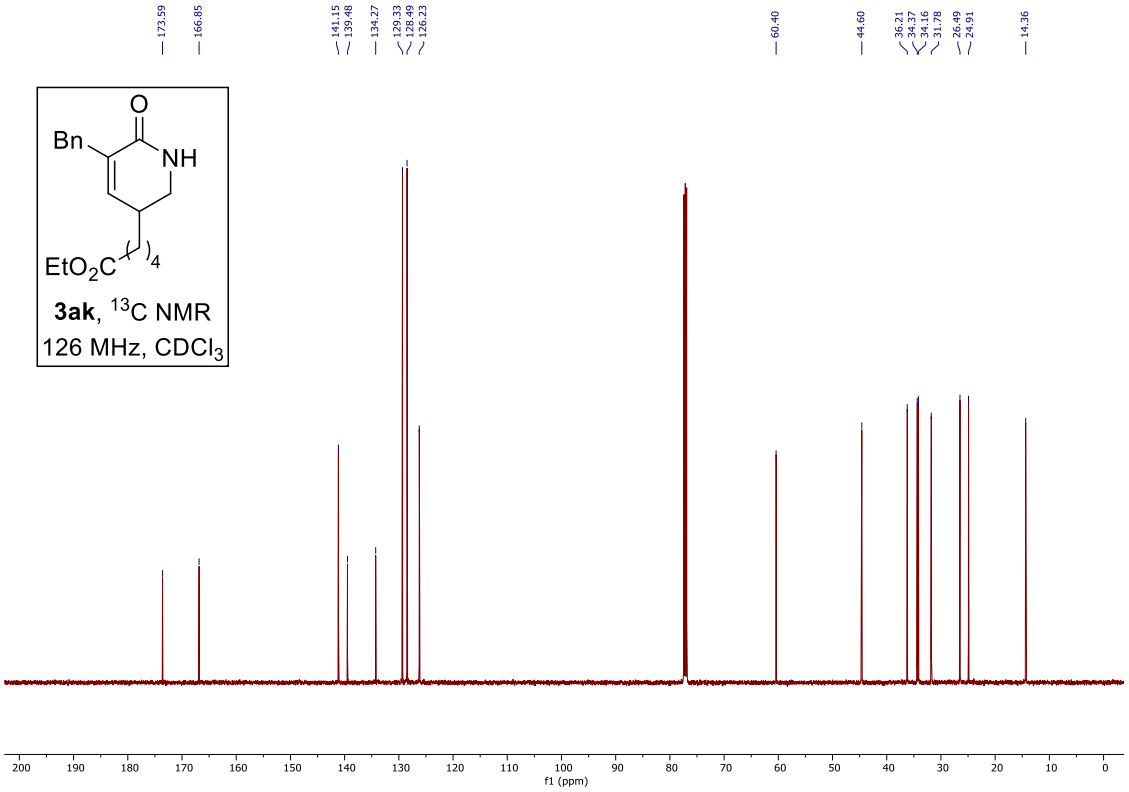

166.82
140.90
139.41
134.45
129.34
128.51
126.26
77.16
CDCl3
44.56
36.21
34.40
33.54
32.58
31.23
25.54
O
Bn
NH
Br
4
3aj, 13C NMR
126 MHz, CDCl3
f1 (ppm)

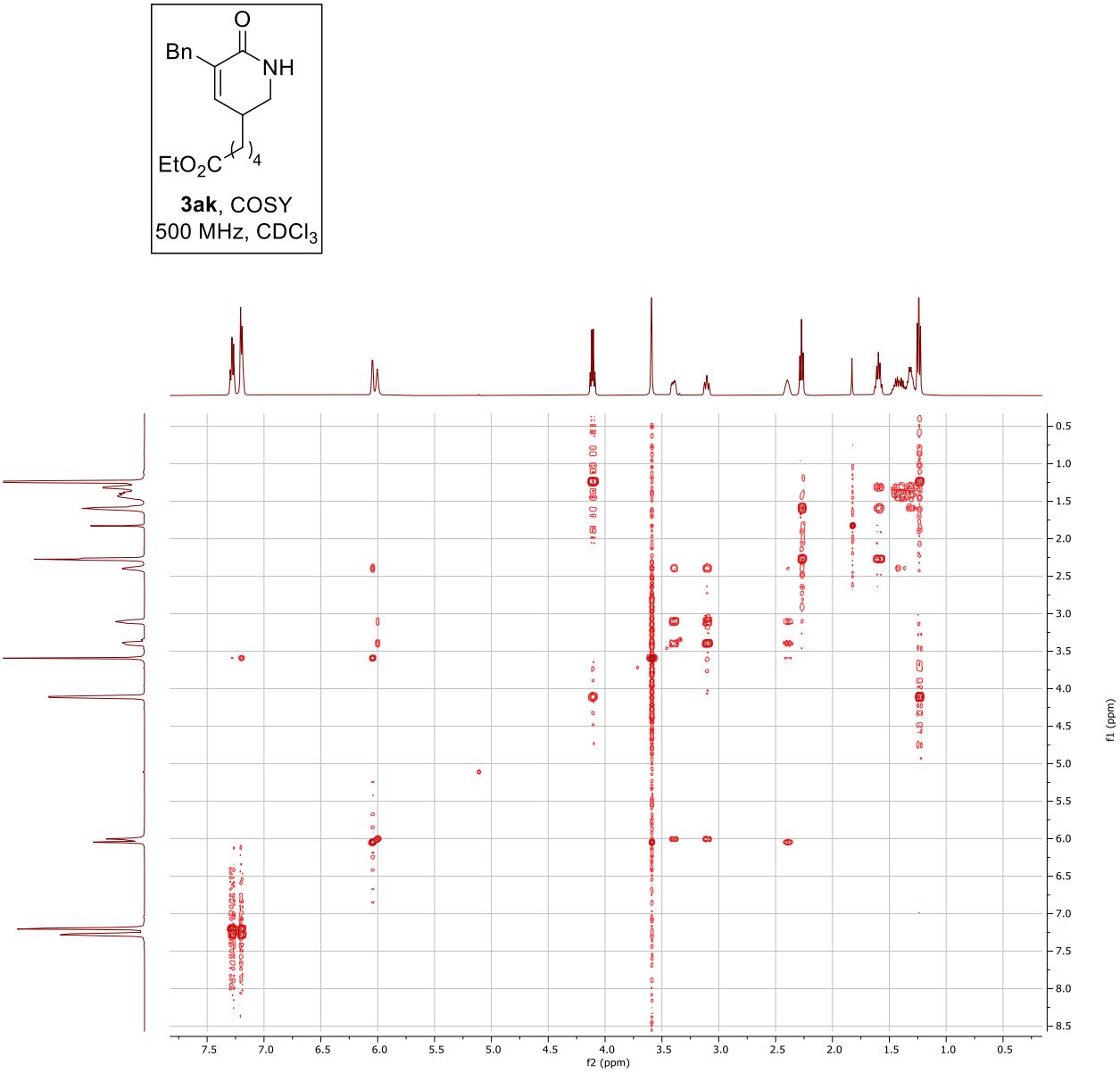


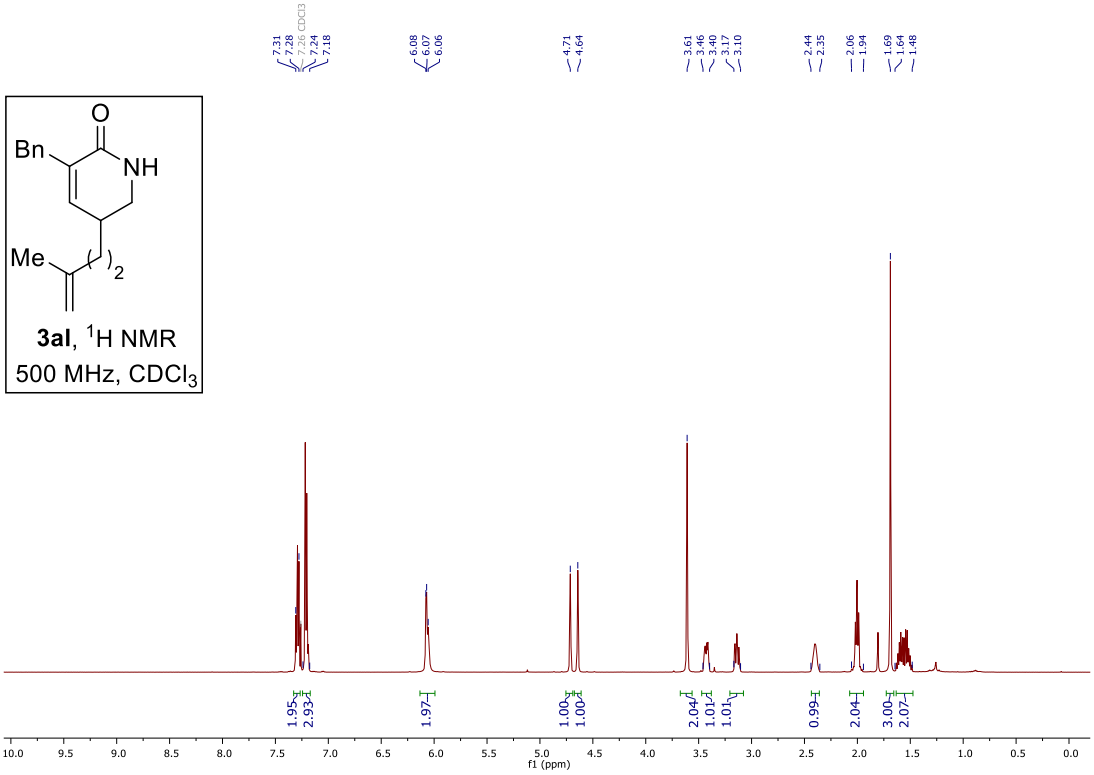
3aj, COSY
500 MHz, $CDCl_3$

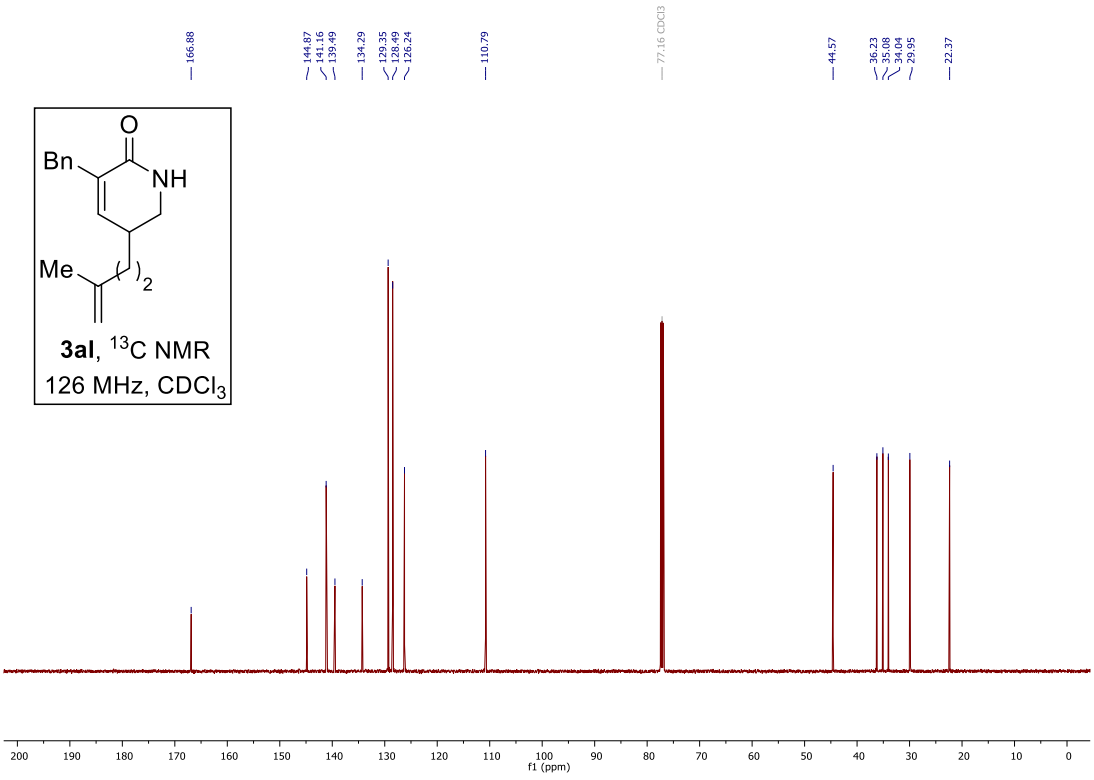


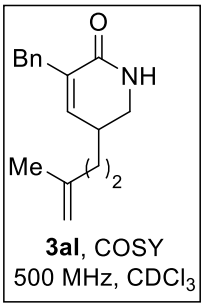

Bn
NH
O
EtO2C
4
3ak, 1H NMR
500 MHz, CDCl3
f1 (ppm)


Bn
NH
O
EtO2C
4
3ak, 13C NMR
126 MHz, CDCl3
f1 (ppm)

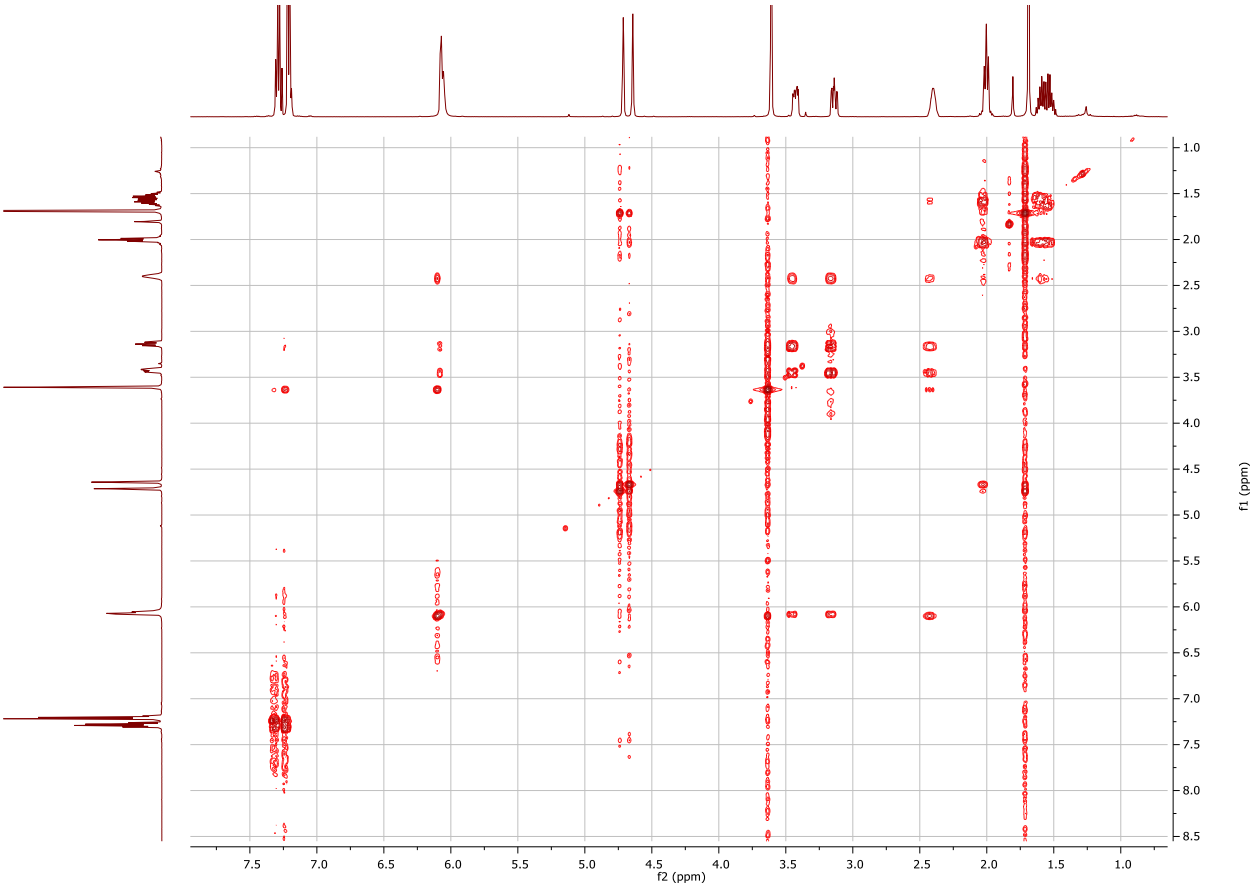

O
Bn
NH
EtO2C
4
3ak, COSY
500 MHz, CDCl3
f2 (ppm)
f1 (ppm)

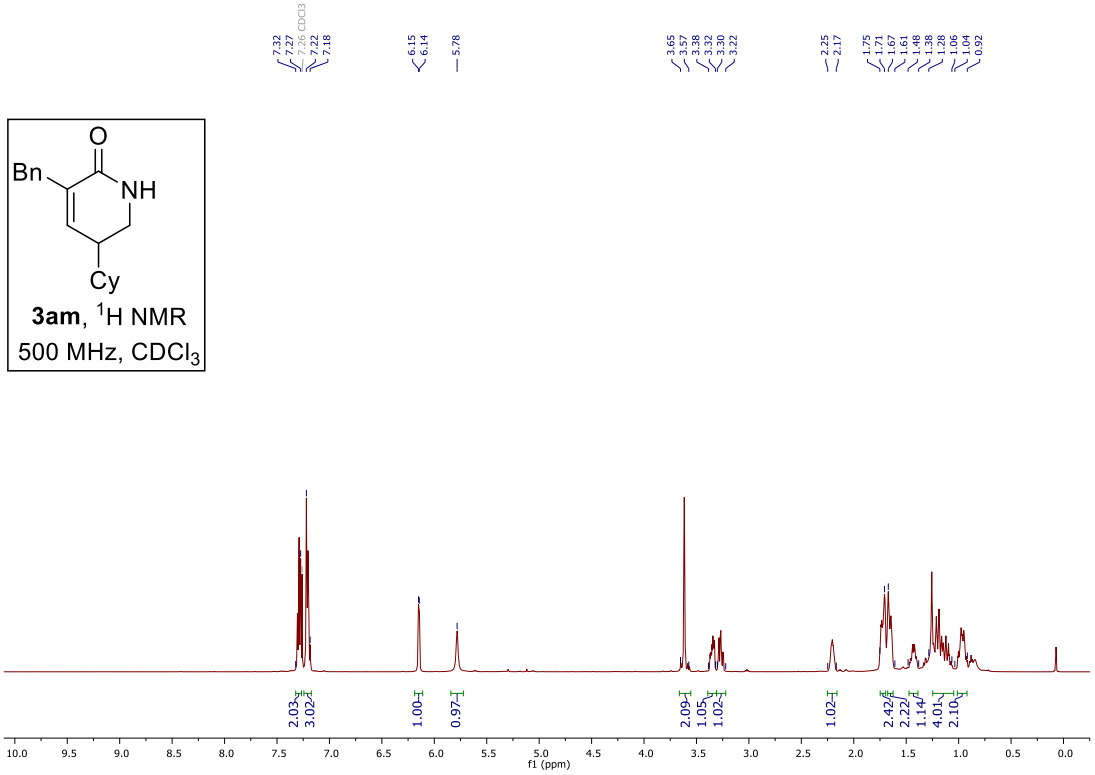

Bn
NH
O
Me
2
3al, 1H NMR
500 MHz, CDCl3
7.31
7.28
7.26 CDCl3
7.24
7.18
6.08
6.07
6.06
4.71
4.64
3.61
3.46
3.40
3.17
3.10
2.44
2.35
2.06
1.94
1.69
1.64
1.48
1.95
2.93
1.97
1.00
1.00
2.04
1.01
1.01
0.99
2.04
3.00
2.07
f1 (ppm)

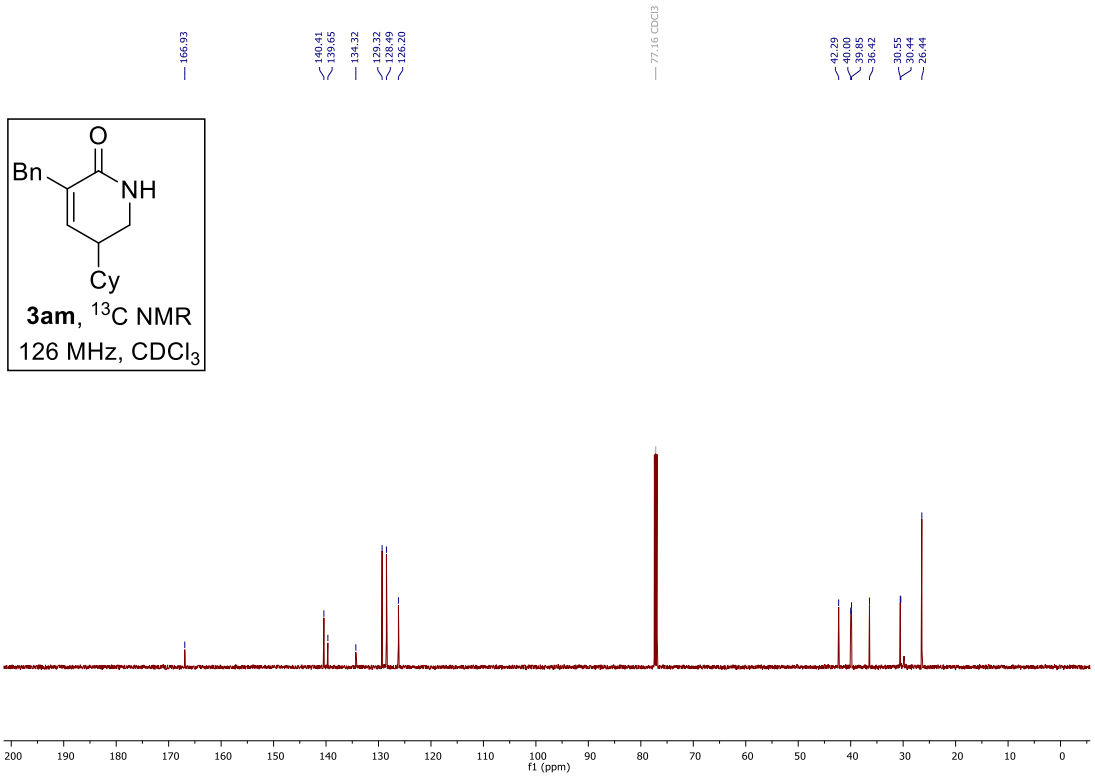

Bn
NH
O
Me
2
3al, 13C NMR
126 MHz, CDCl3
166.88
144.87
141.16
139.49
134.29
129.35
128.49
126.24
110.79
77.16 CDCl3
44.57
36.23
35.08
34.04
29.95
22.37
f1 (ppm)

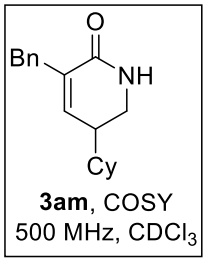


3al, COSY
500 MHz, $CDCl_3$

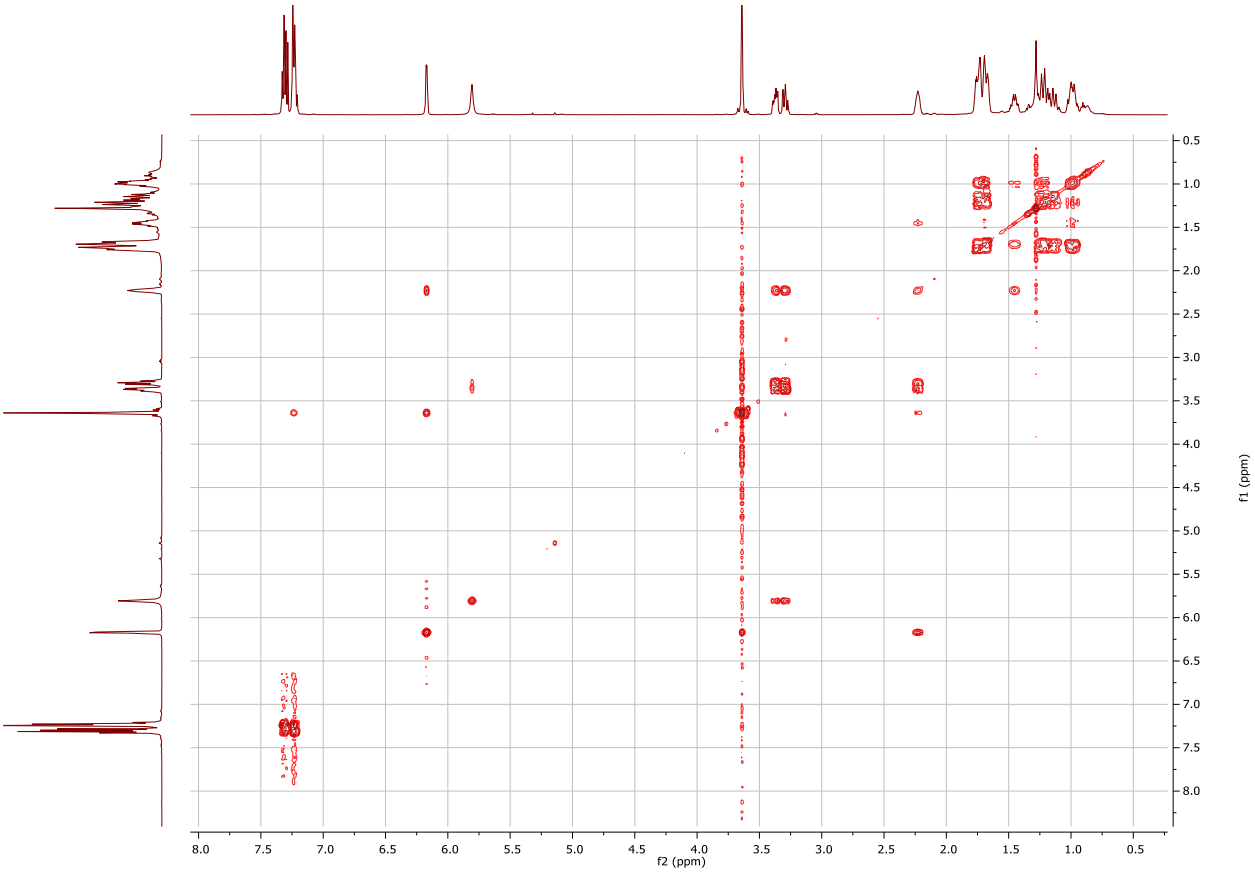


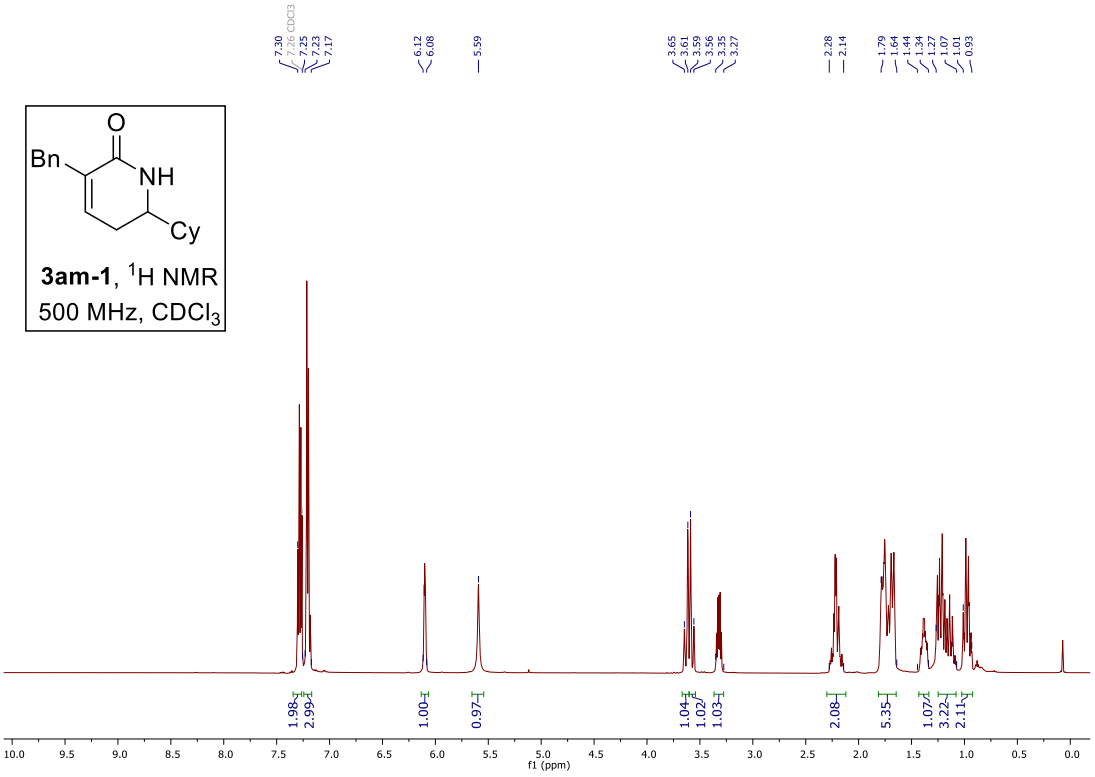

7.32
7.27
7.26 CDCl3
7.22
7.18
6.15
6.14
5.78
3.65
3.57
3.38
3.32
3.30
3.22
2.25
2.17
1.75
1.71
1.67
1.61
1.48
1.38
1.28
1.06
1.04
0.92
Bn
NH
Cy
3am, 1H NMR
500 MHz, CDCl3
2.03
3.02
1.00
0.97
2.09
1.05
1.02
1.02
2.42
2.22
1.14
4.01
2.10
f1 (ppm)

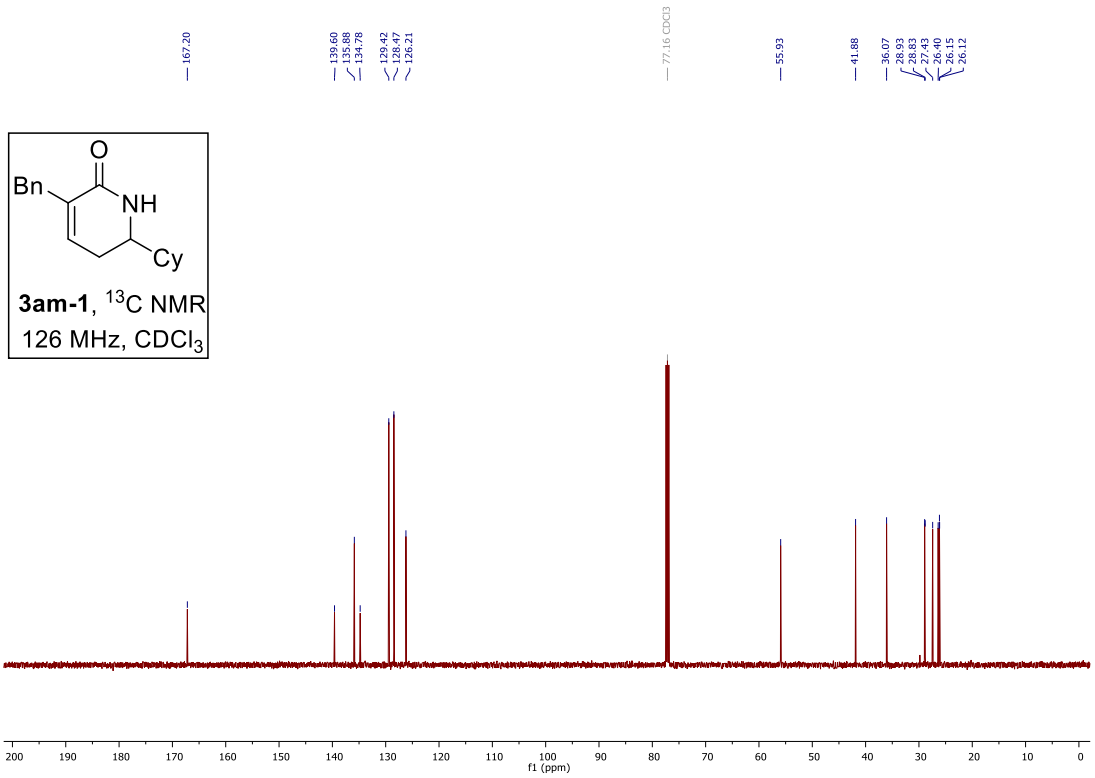

166.93
140.41
139.65
134.32
129.32
128.49
126.20
77.16 CDCl3
42.29
40.00
39.85
36.42
30.55
30.44
26.44
Bn
NH
Cy
3am, 13C NMR
126 MHz, CDCl3
f1 (ppm)

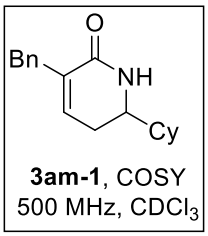


3am, COSY
500 MHz, $CDCl_3$

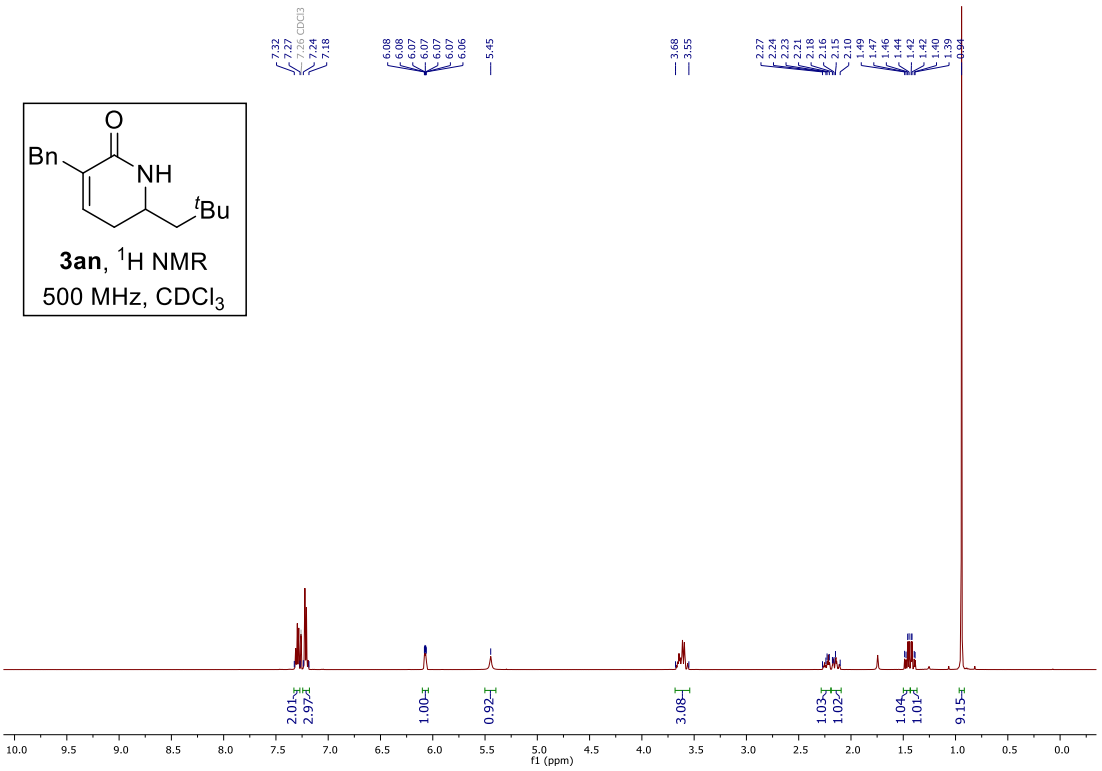


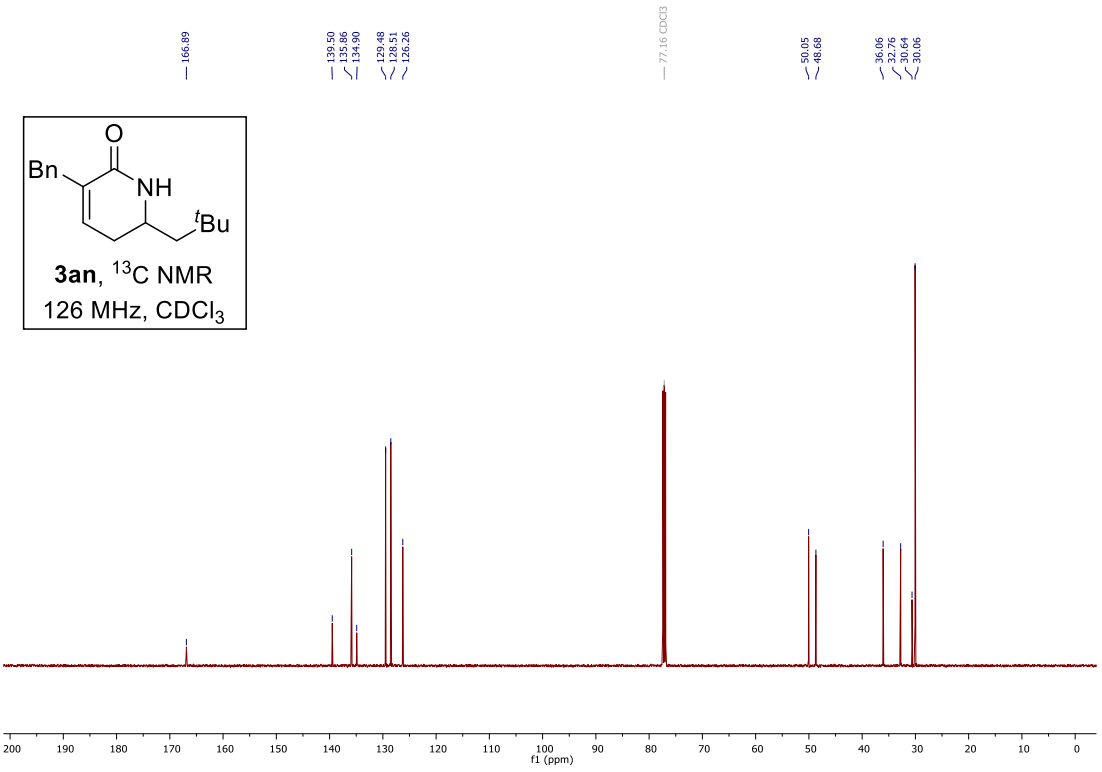

Bn
NH
Cy
O
3am-1, 1H NMR
500 MHz, CDCl3
f1 (ppm)

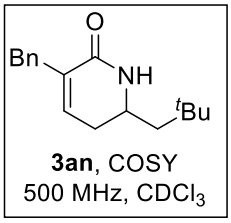

Bn
NH
Cy
O
3am-1, 13C NMR
126 MHz, CDCl3
f1 (ppm)

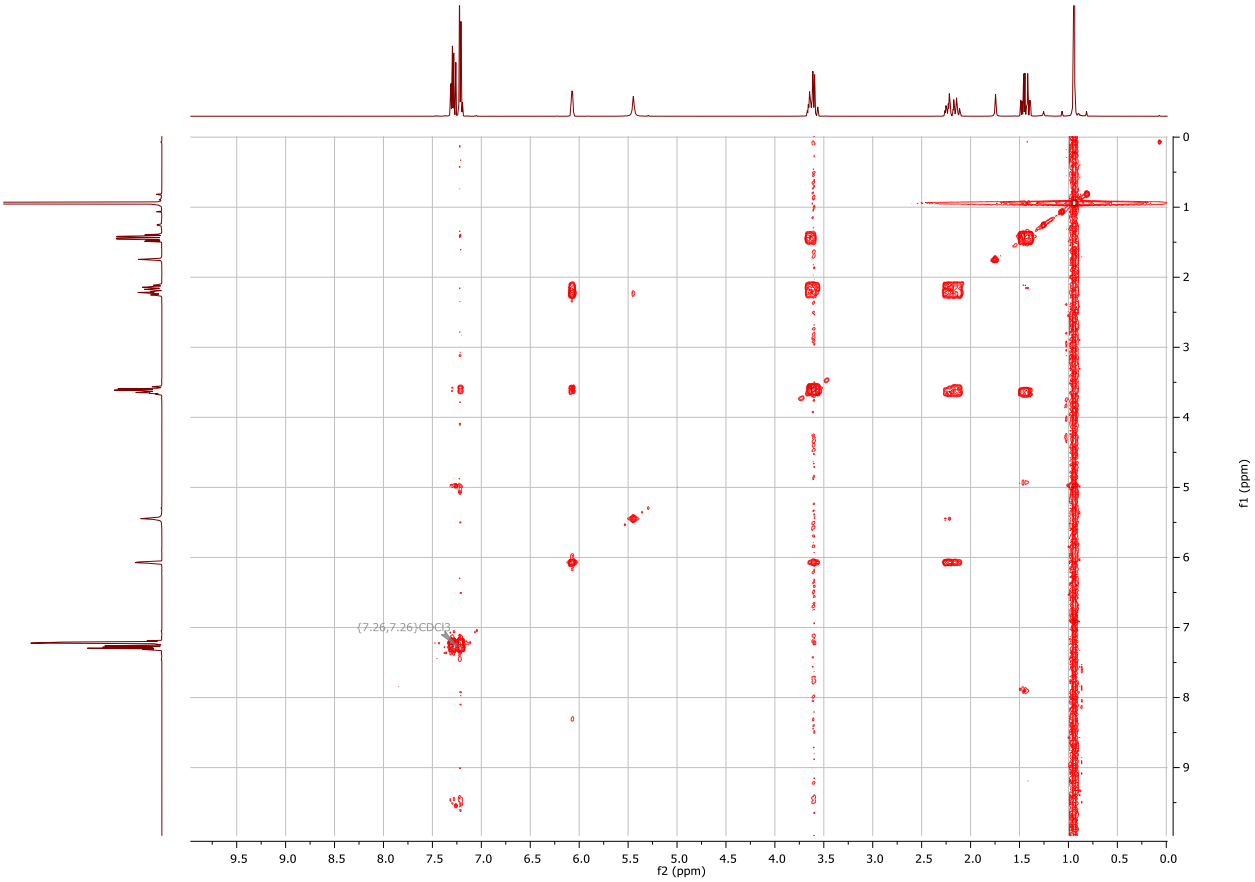


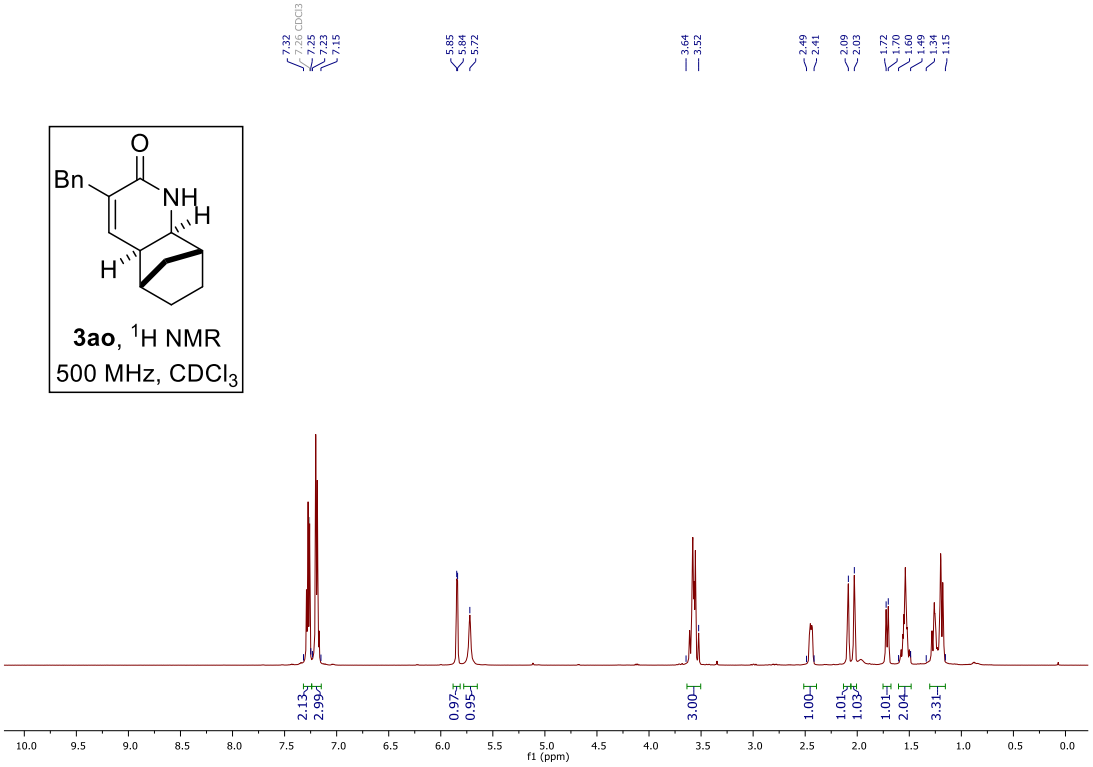
3am-1, COSY
500 MHz, $CDCl_3$

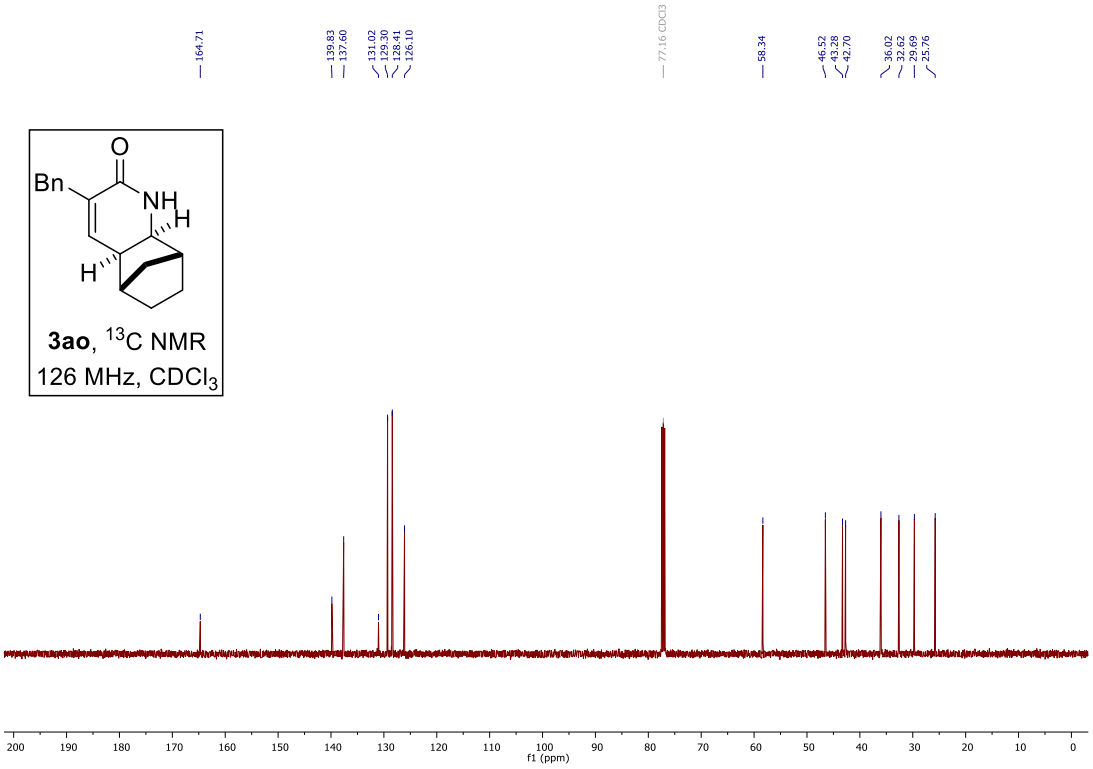

Bn
NH
tBu
3an, 1H NMR
500 MHz, CDCl3
f1 (ppm)

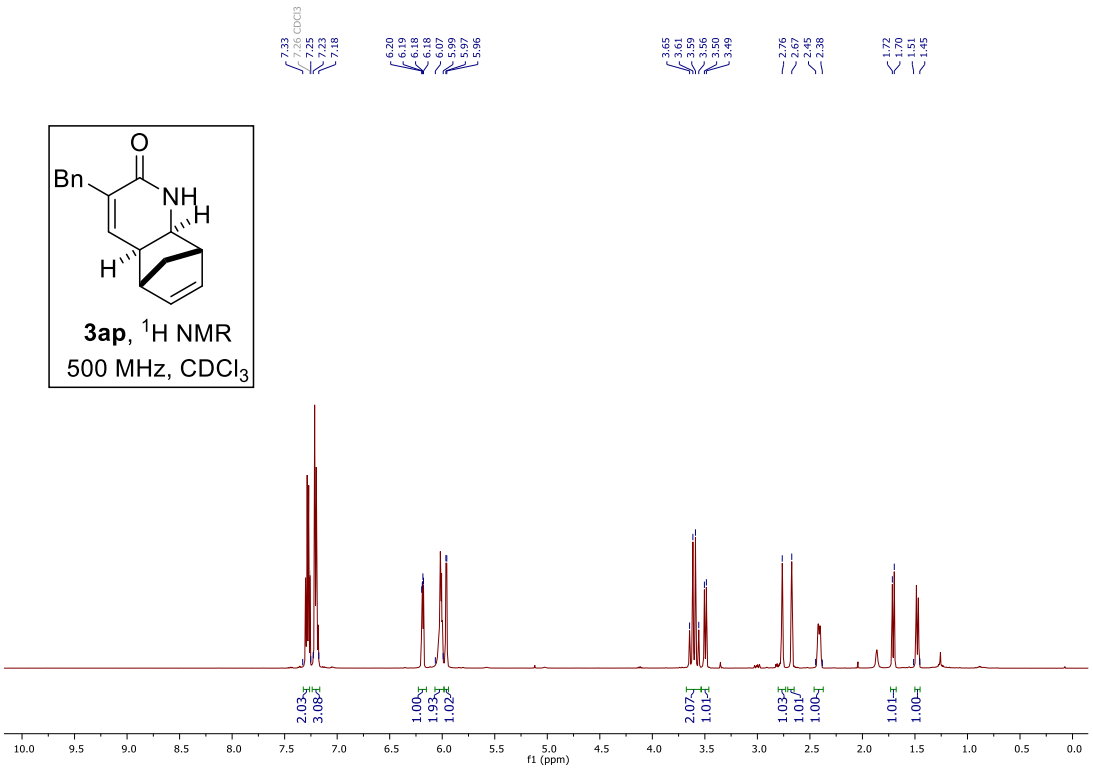

166.89
139.50
135.86
134.90
129.48
128.51
126.26
77.16 CDCl3
50.05
48.68
36.06
32.76
30.64
30.06
O
Bn
NH
tBu
3an, 13C NMR
126 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

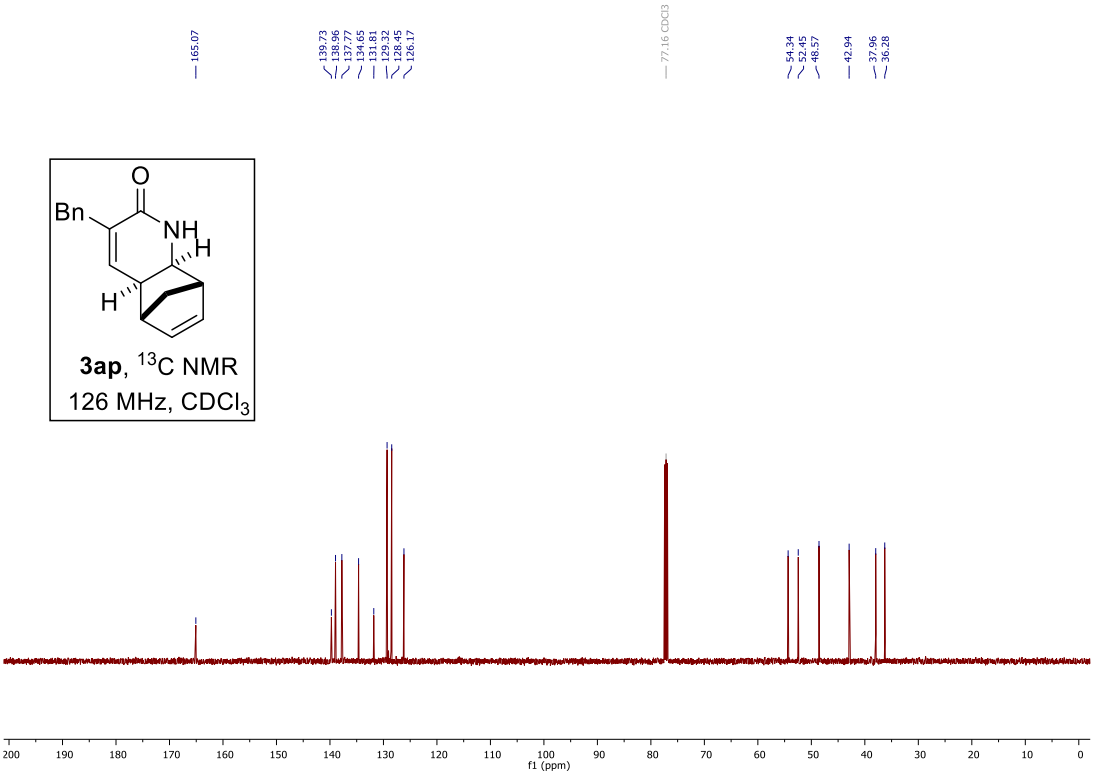

O
Bn
NH
tBu
3an, COSY
500 MHz, CDCl3

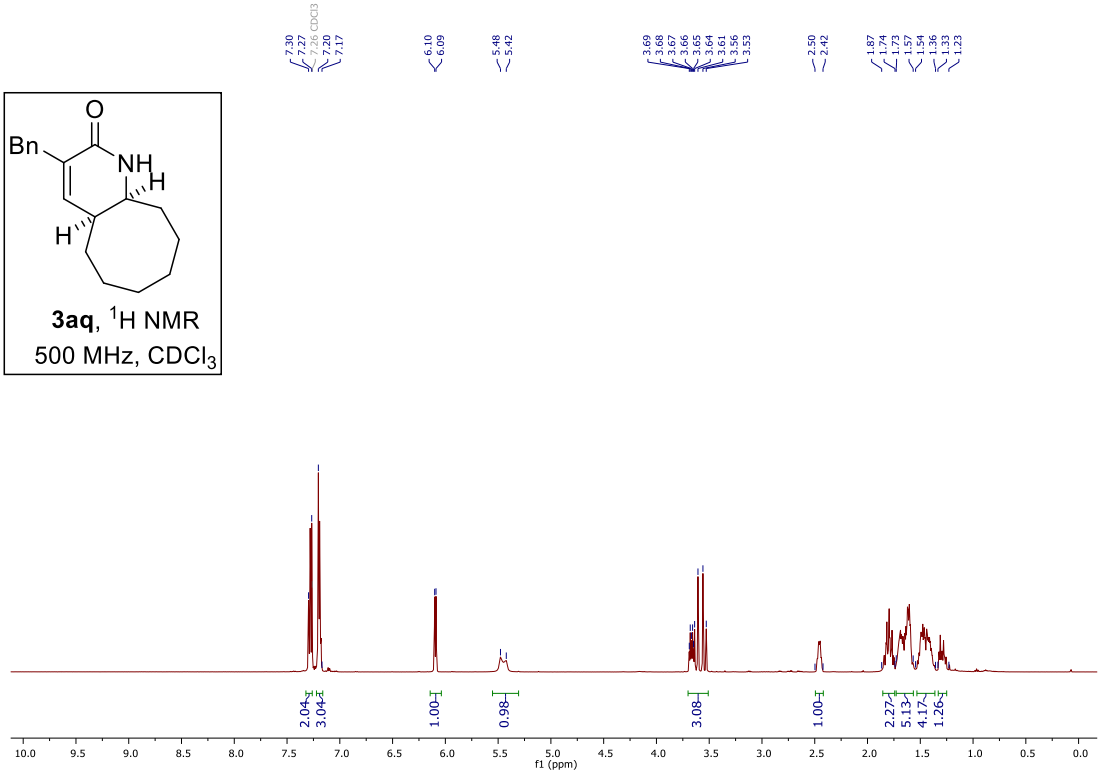

{7.26,7.26}CDCl3
f2 (ppm)
f1 (ppm)

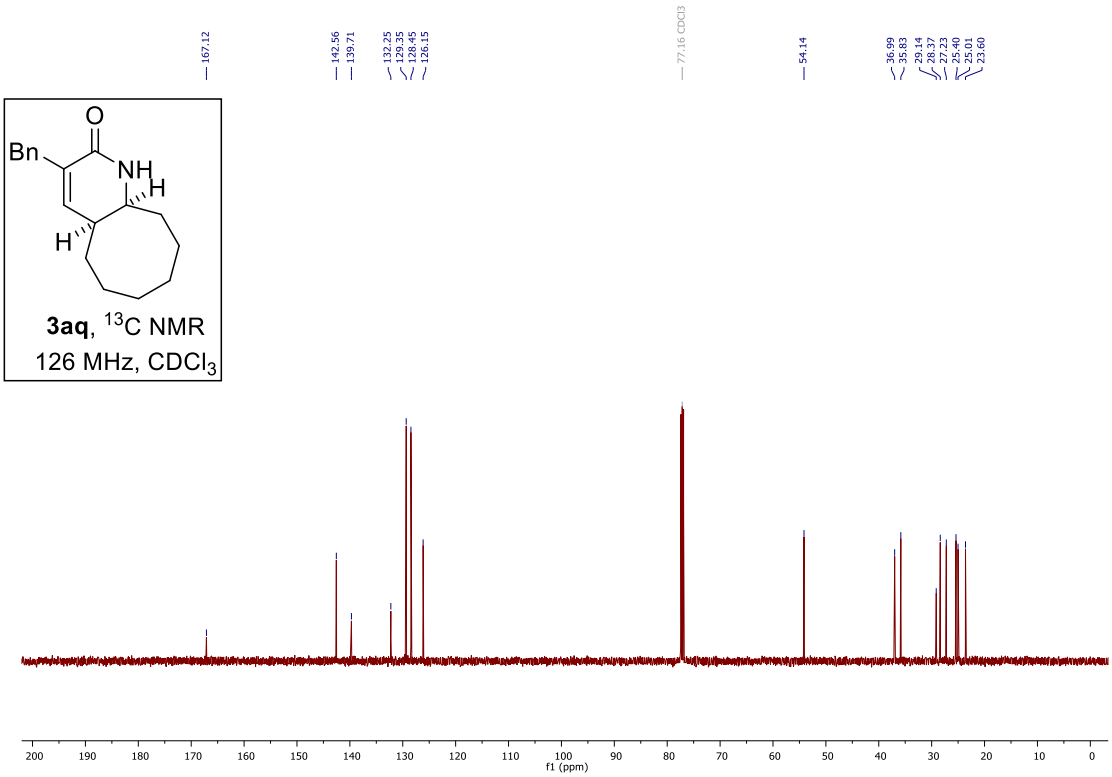

7.32
7.26 CDCl3
7.25
7.23
7.15
5.85
5.84
5.72
3.64
3.52
2.49
2.41
2.09
2.03
1.72
1.70
1.60
1.49
1.34
1.15
O
Bn
NH
H
H
3ao, 1H NMR
500 MHz, CDCl3
2.13
2.99
0.97
0.95
3.00
1.00
1.01
1.03
1.01
2.04
3.31
f1 (ppm)

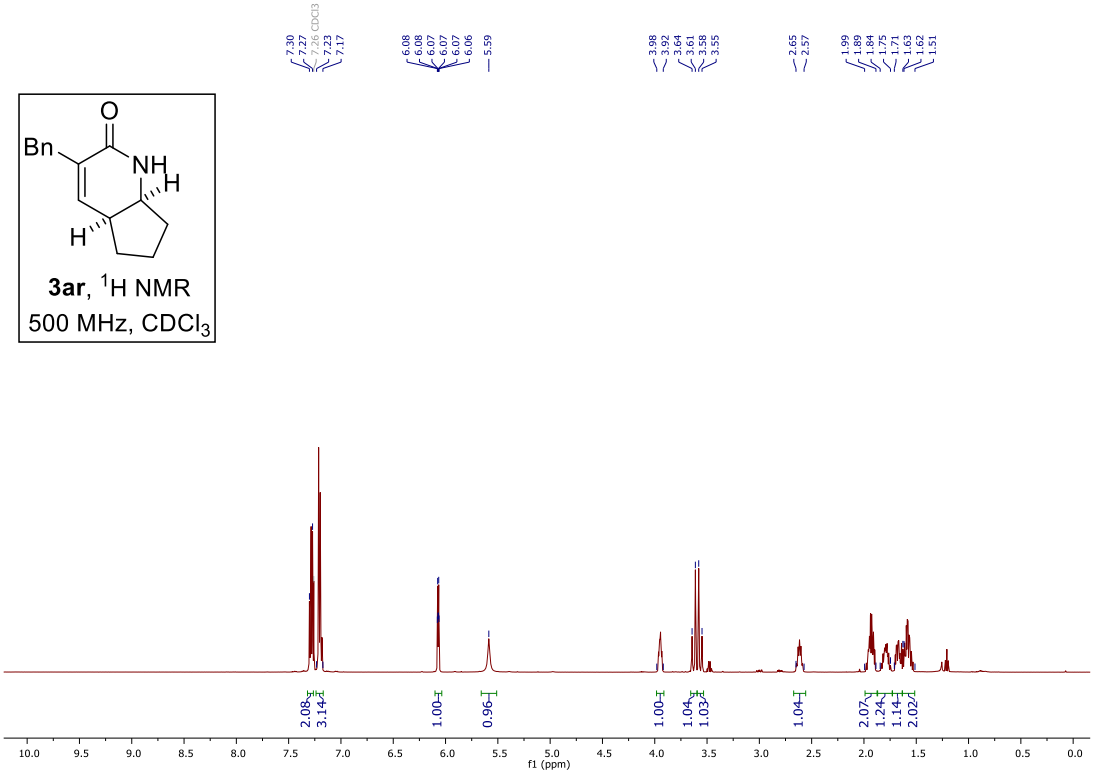

164.71
139.83
137.60
131.02
129.30
128.41
126.10
77.16 CDCl3
58.34
46.52
43.28
42.70
36.02
32.62
29.69
25.76
O
Bn
NH
H
H
3ao, 13C NMR
126 MHz, CDCl3
f1 (ppm)

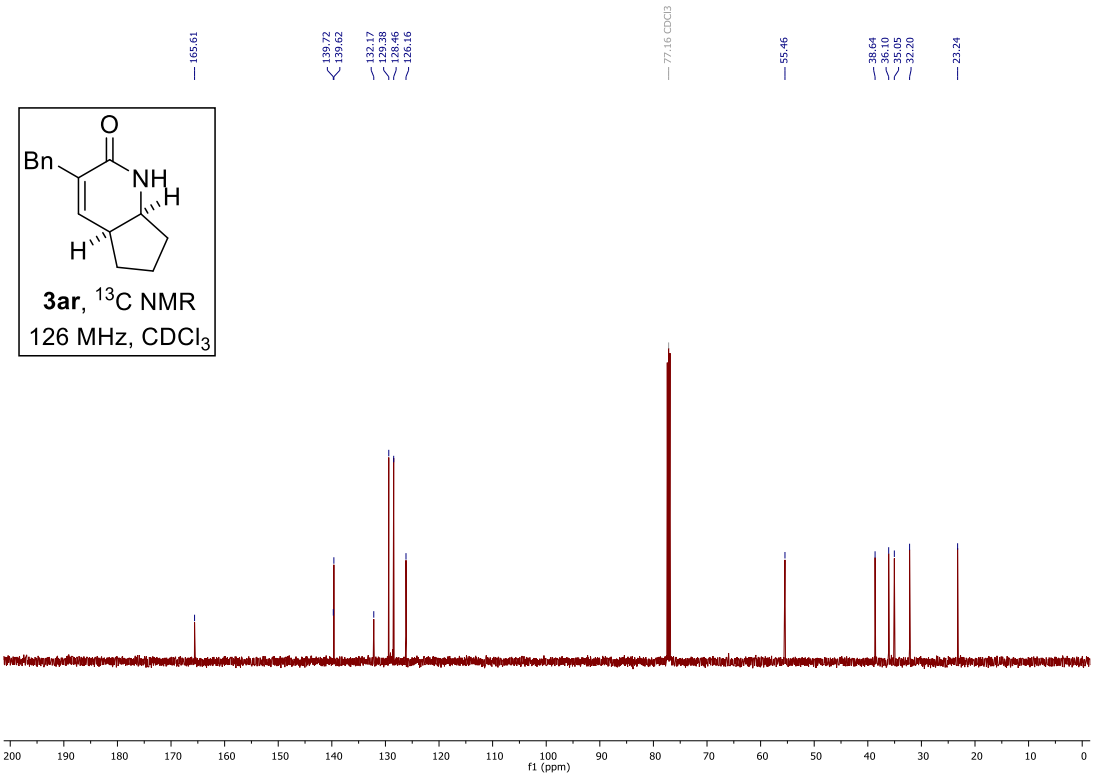

7.33
7.26 CDCl3
7.25
7.23
7.18
6.20
6.19
6.18
6.18
6.07
5.99
5.97
5.96
3.65
3.61
3.59
3.56
3.50
3.49
2.76
2.67
2.45
2.38
1.72
1.70
1.51
1.45
O
Bn
NH
H
H
3ap, 1H NMR
500 MHz, CDCl3
2.03
3.08
1.00
1.93
1.02
2.07
1.01
1.03
1.01
1.00
1.01
1.00
f1 (ppm)


165.07
139.73
138.96
137.77
134.65
131.81
129.32
128.45
126.17
77.16 CDCl3
54.34
52.45
48.57
42.94
37.96
36.28
O
Bn
NH
H
H
3ap, 13C NMR
126 MHz, CDCl3
f1 (ppm)

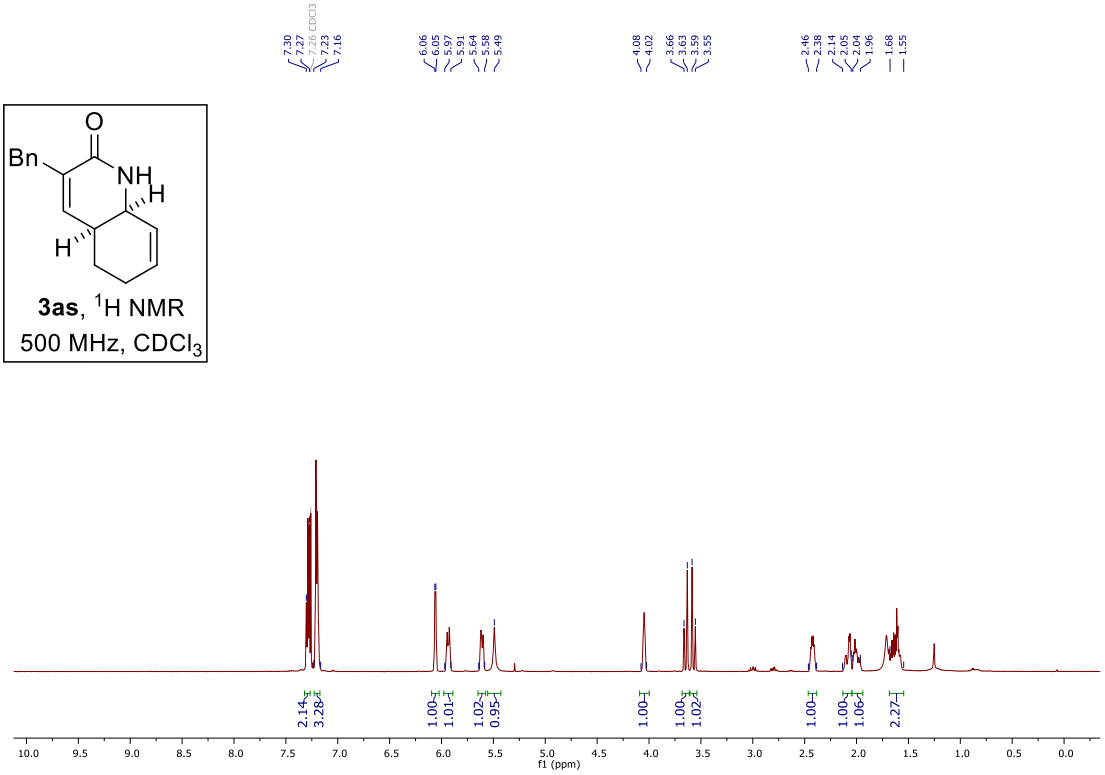

7.30
7.27
7.26 CDCl3
7.20
7.17
6.10
6.09
5.48
5.42
3.69
3.68
3.67
3.66
3.65
3.64
3.61
3.56
3.53
2.50
2.42
1.87
1.74
1.73
1.57
1.54
1.36
1.33
1.23
O
Bn
NH
H
H
3aq, 1H NMR
500 MHz, CDCl3
2.04
3.04
1.00
0.98
3.08
1.00
2.27
5.13
4.17
1.26
f1 (ppm)


167.12
142.56
139.71
132.25
129.35
128.45
126.15
77.16 CDCl3
54.14
36.99
35.83
29.14
28.37
27.23
25.40
25.01
23.60
O
Bn
NH
H
H
3aq, 13C NMR
126 MHz, CDCl3
f1 (ppm)

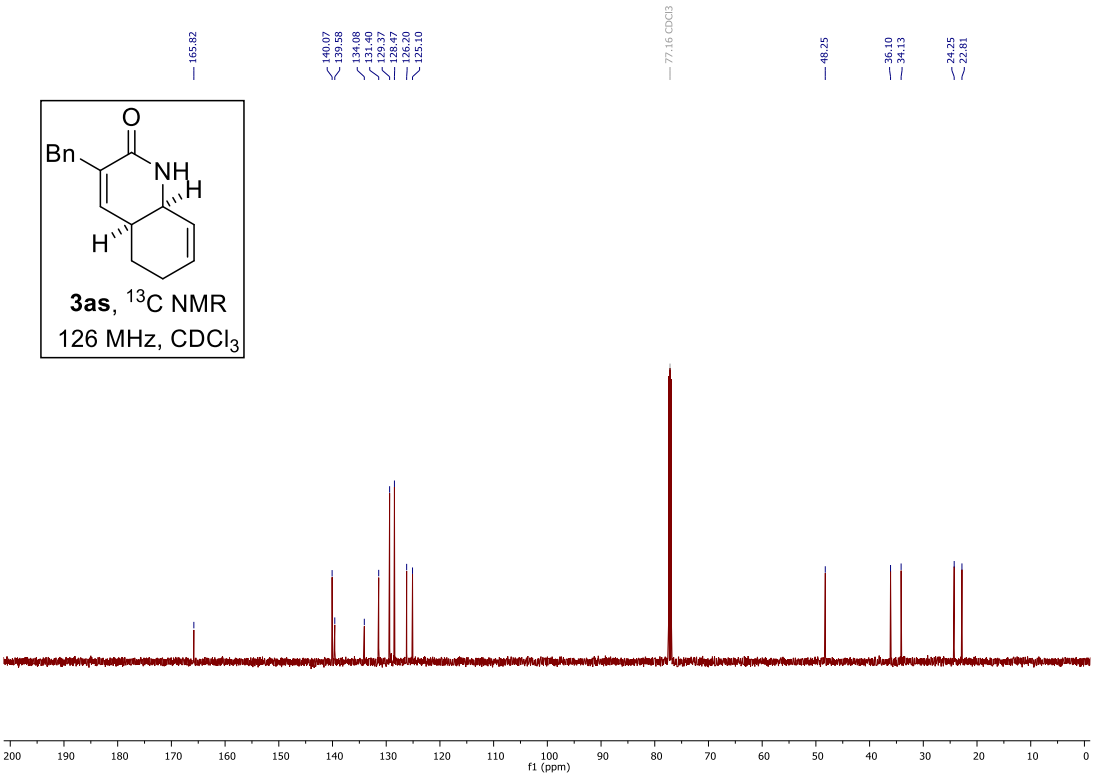

7.30
7.27
7.26 CDCl3
7.23
7.17
6.08
6.08
6.07
6.07
6.07
6.06
5.59
3.98
3.92
3.64
3.61
3.58
3.55
2.65
2.57
1.99
1.89
1.84
1.75
1.71
1.63
1.62
1.51
O
Bn
NH
H
H
3ar, 1H NMR
500 MHz, CDCl3
2.08
3.14
1.00
0.96
1.00
1.04
1.03
1.04
2.07
1.24
1.14
2.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

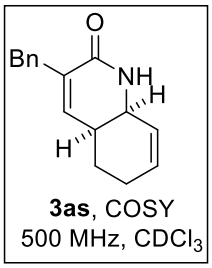

165.61
139.72
139.62
132.17
129.38
128.46
126.16
77.16 CDCl3
55.46
38.64
36.10
35.05
32.20
23.24
O
Bn
NH
H
H
3ar, 13C NMR
126 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

3as, ^{1}H NMR
500 MHz, $CDCl_3$

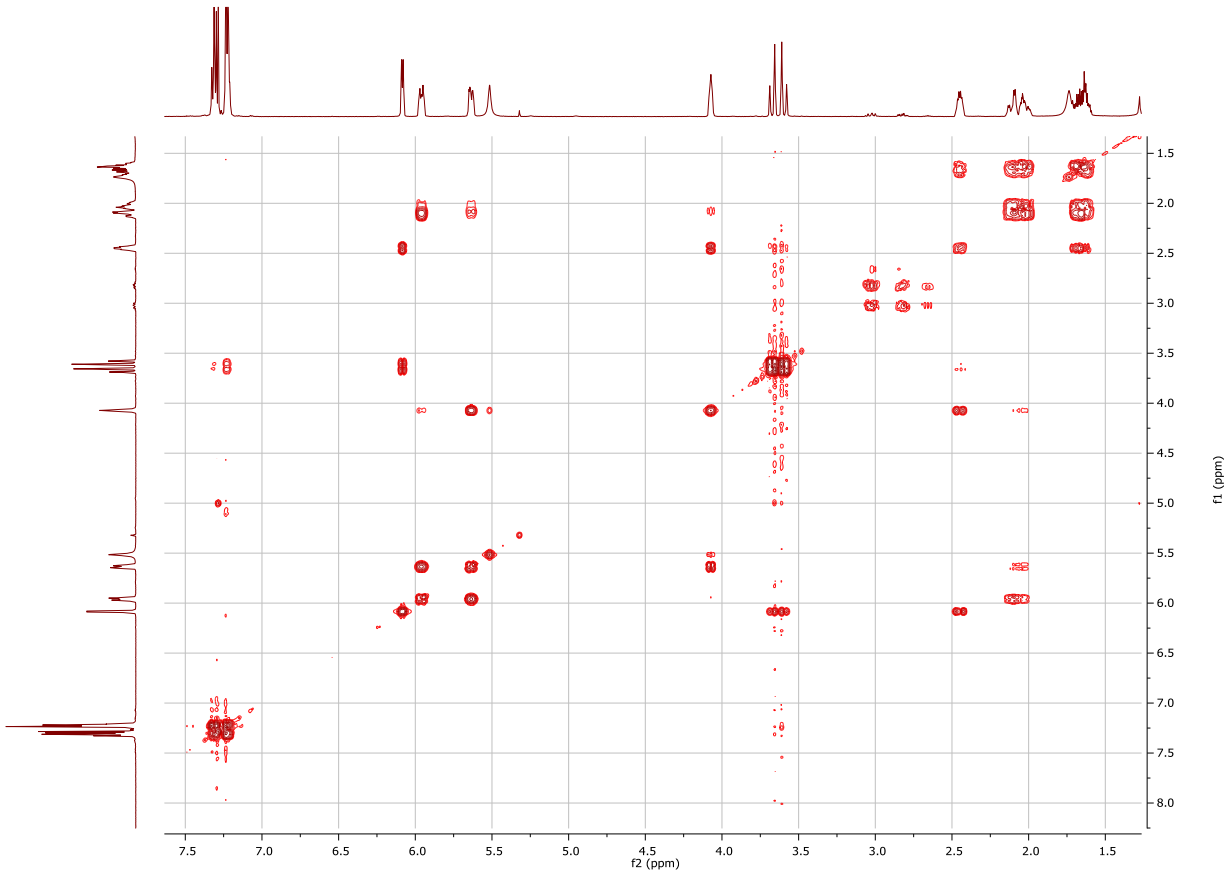


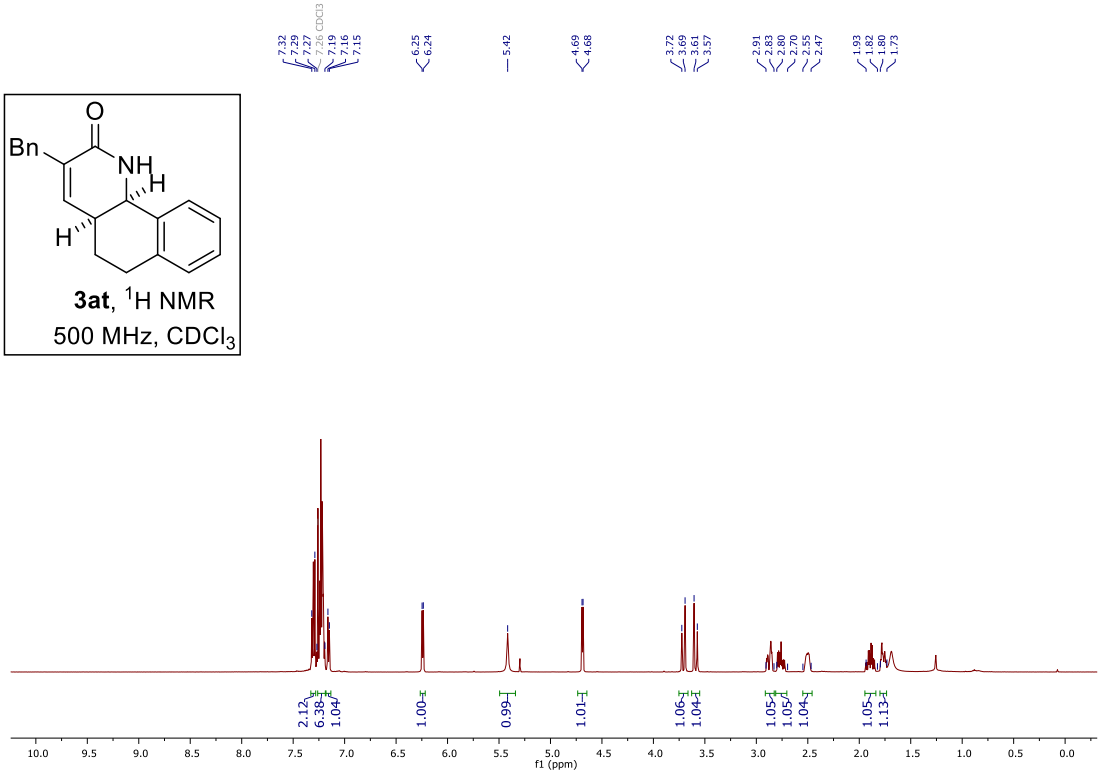
3as, ^{13}C NMR
126 MHz, $CDCl_3$

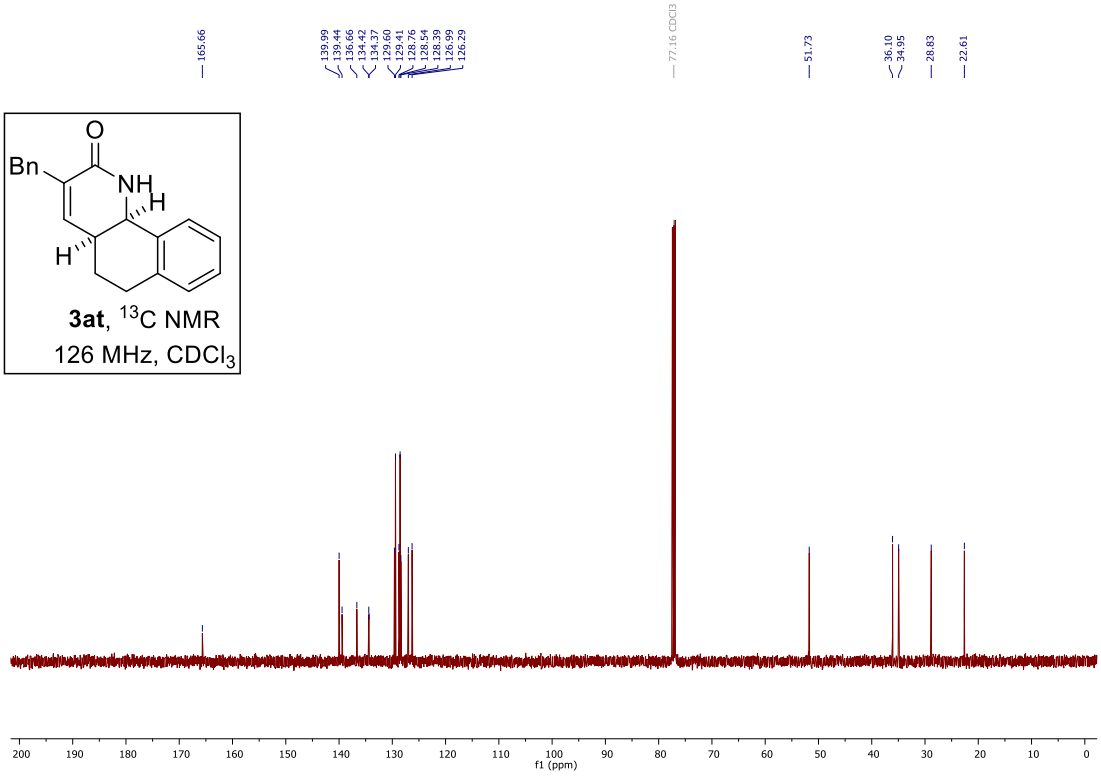


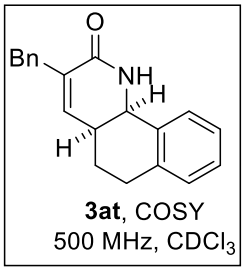


3as, COSY
500 MHz, $CDCl_3$

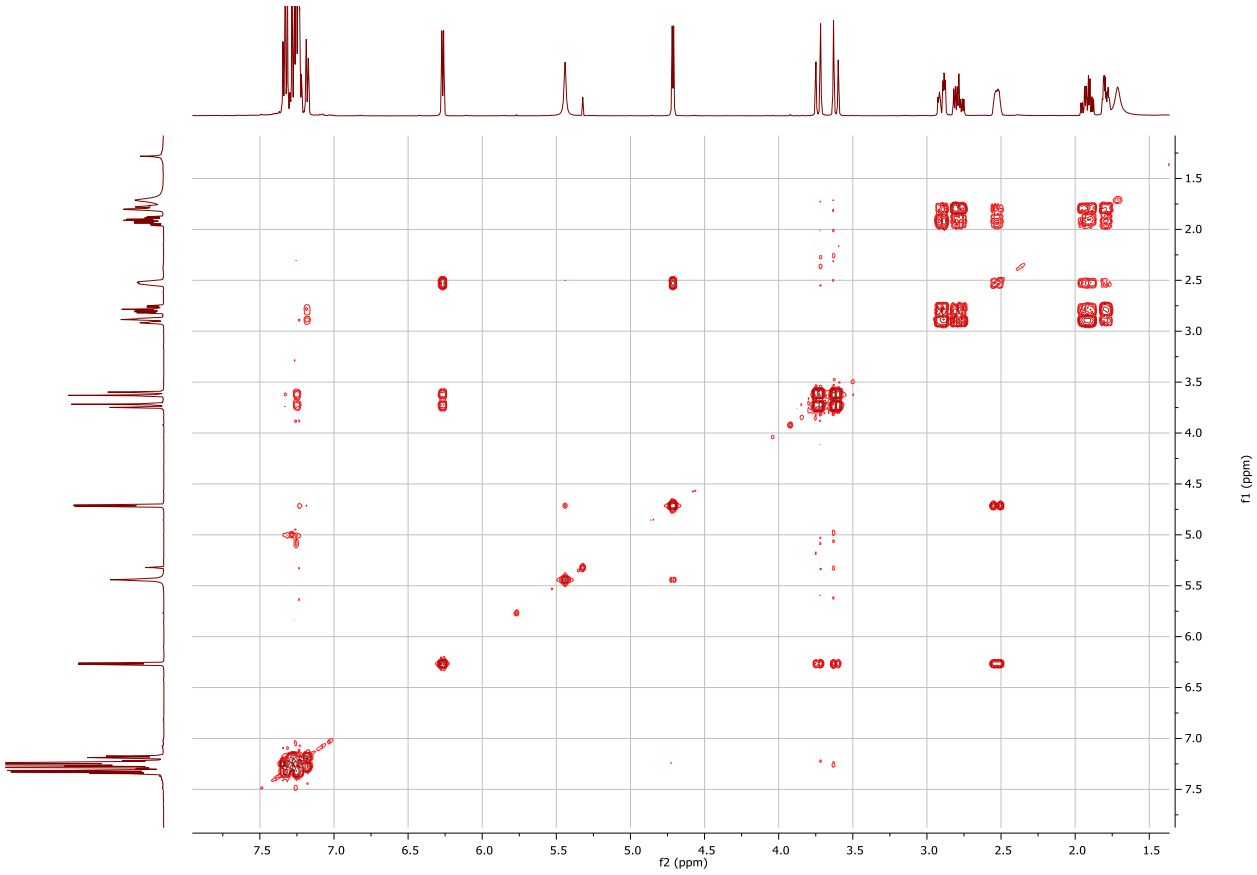


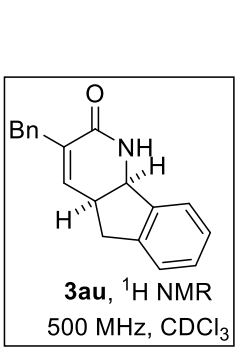

Bn
O
NH
H
H
3at, 1H NMR
500 MHz, CDCl3
f1 (ppm)


Bn
O
NH
H
H
3at, 13C NMR
126 MHz, CDCl3
f1 (ppm)

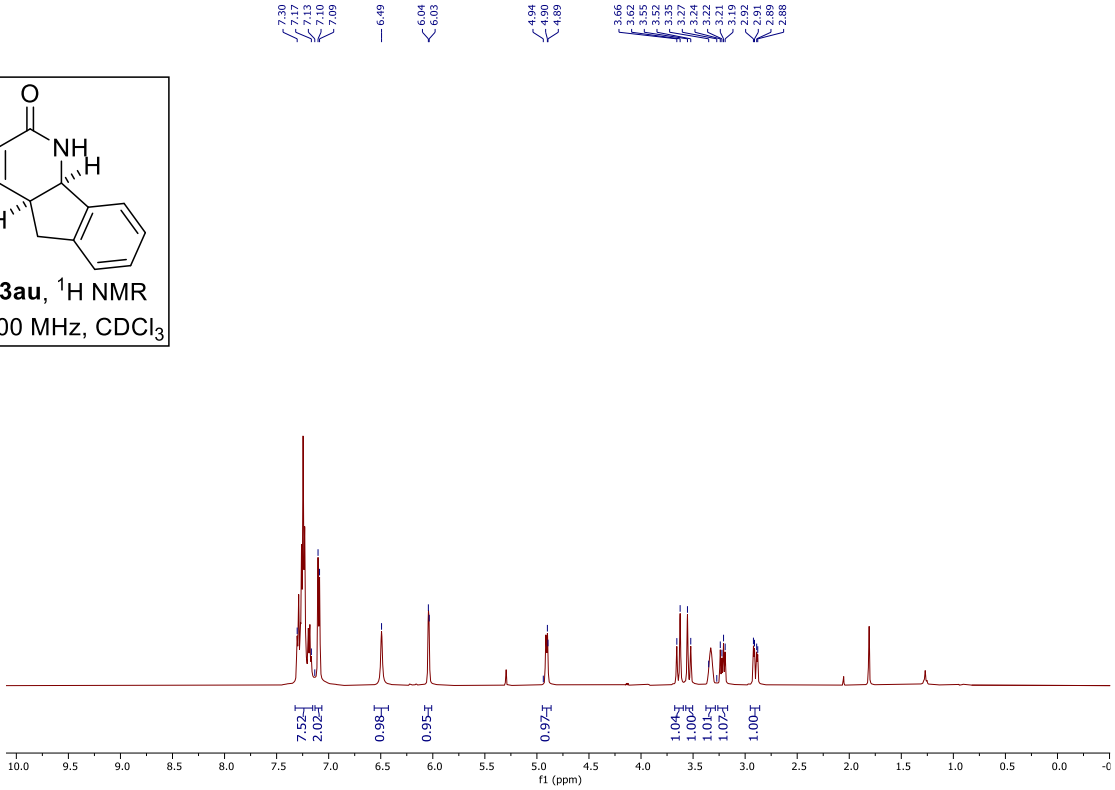


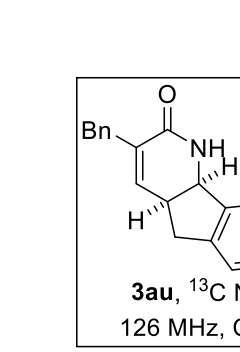
3at, COSY
500 MHz, $CDCl_3$



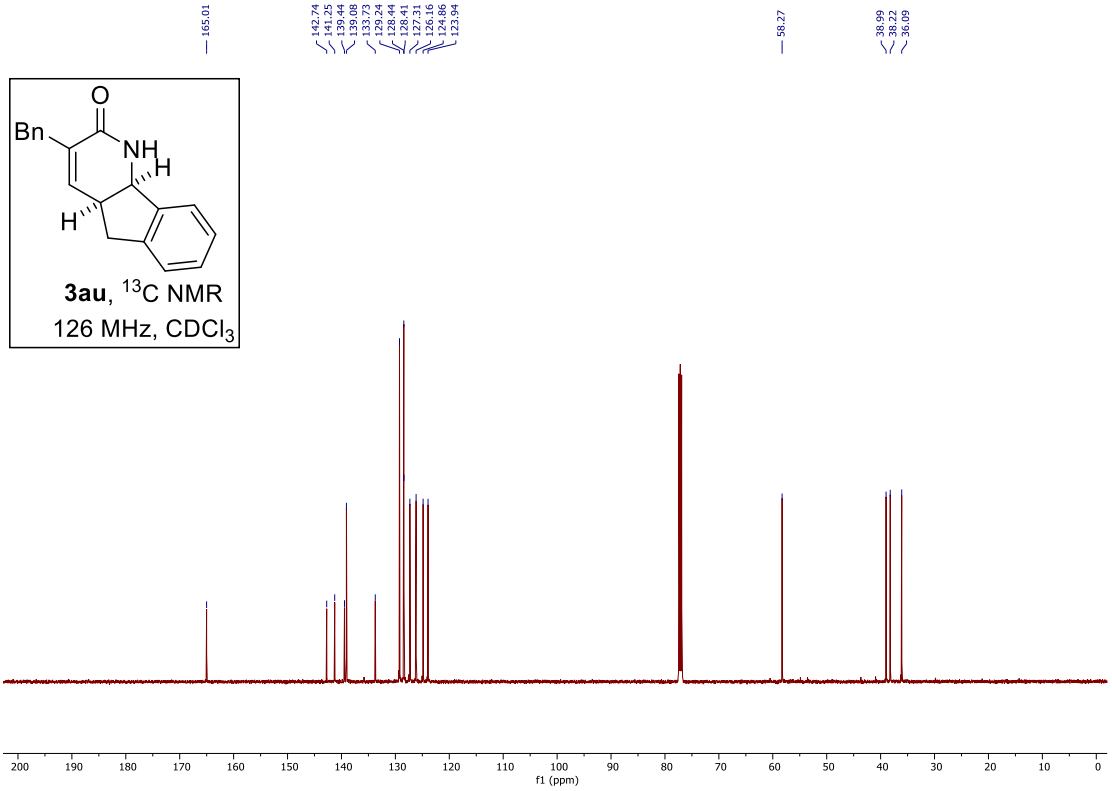


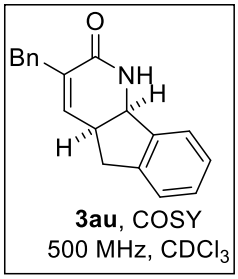
3au, ^{1}H NMR
500 MHz, $CDCl_3$



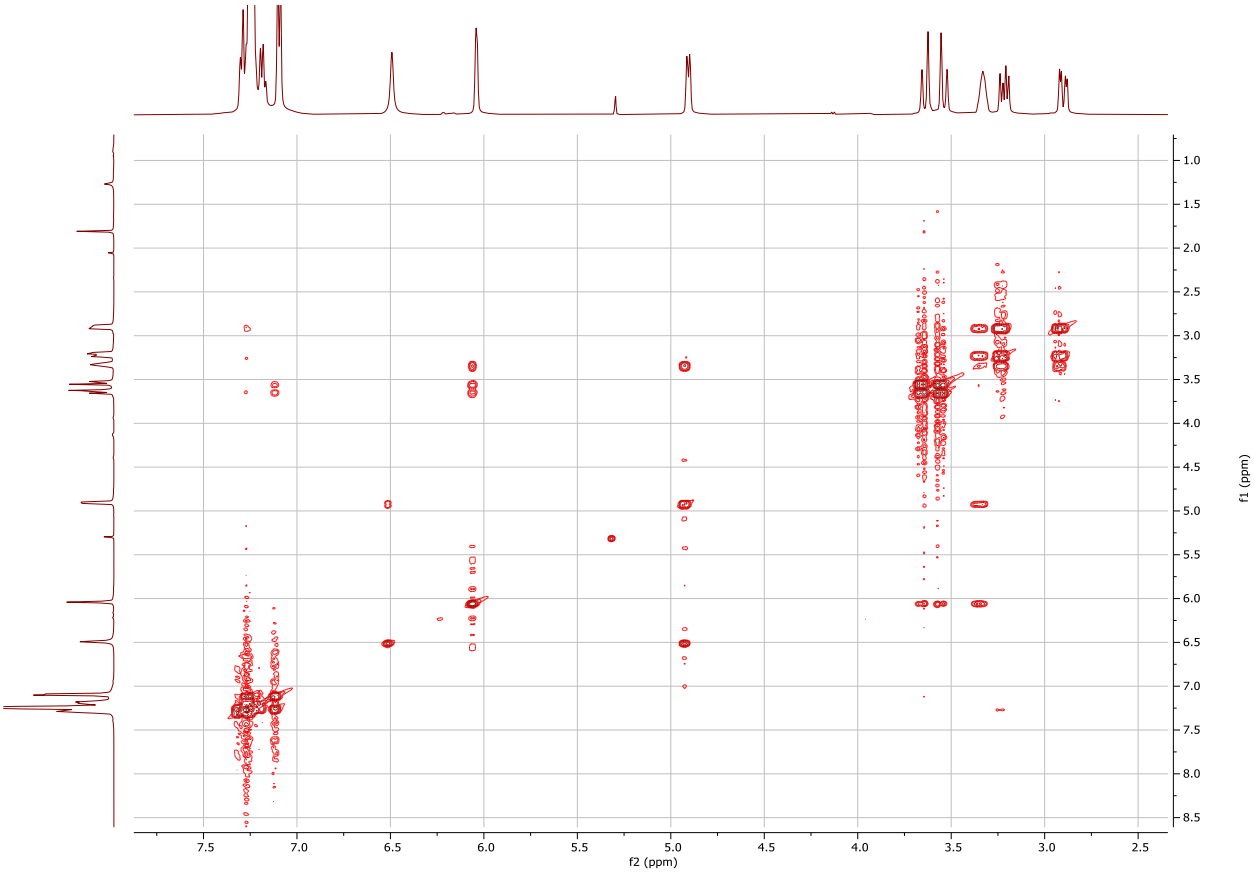


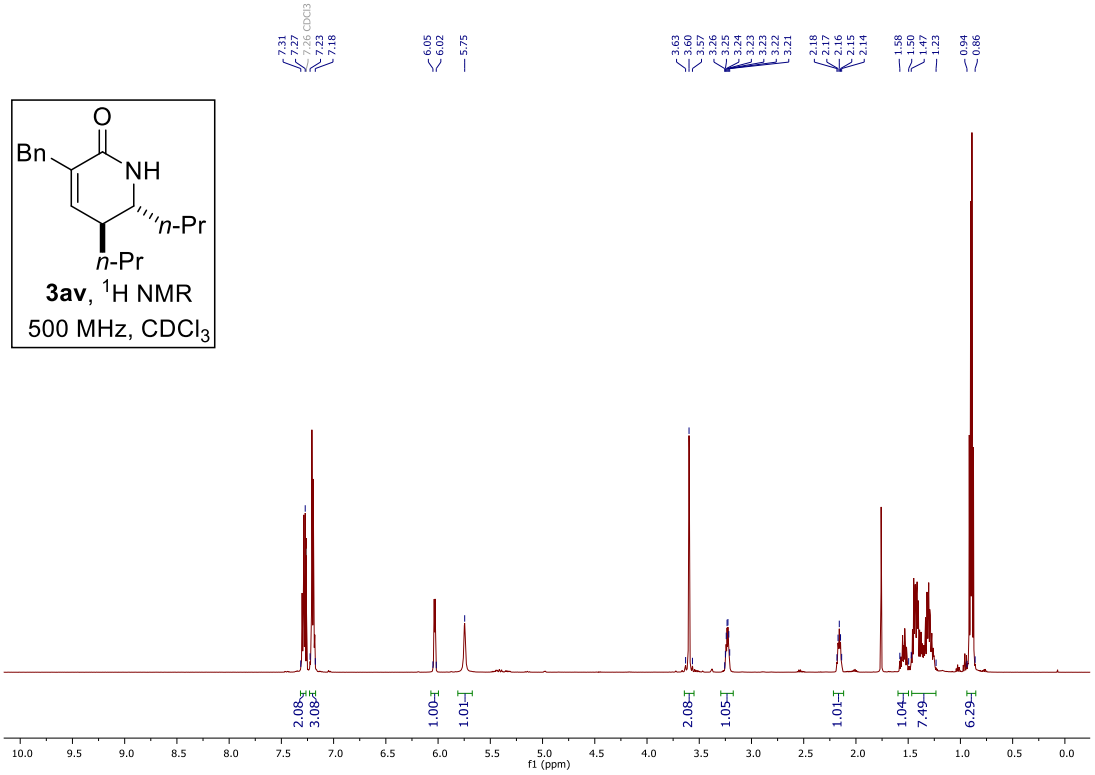
3au, ^{13}C NMR
126 MHz, $CDCl_3$

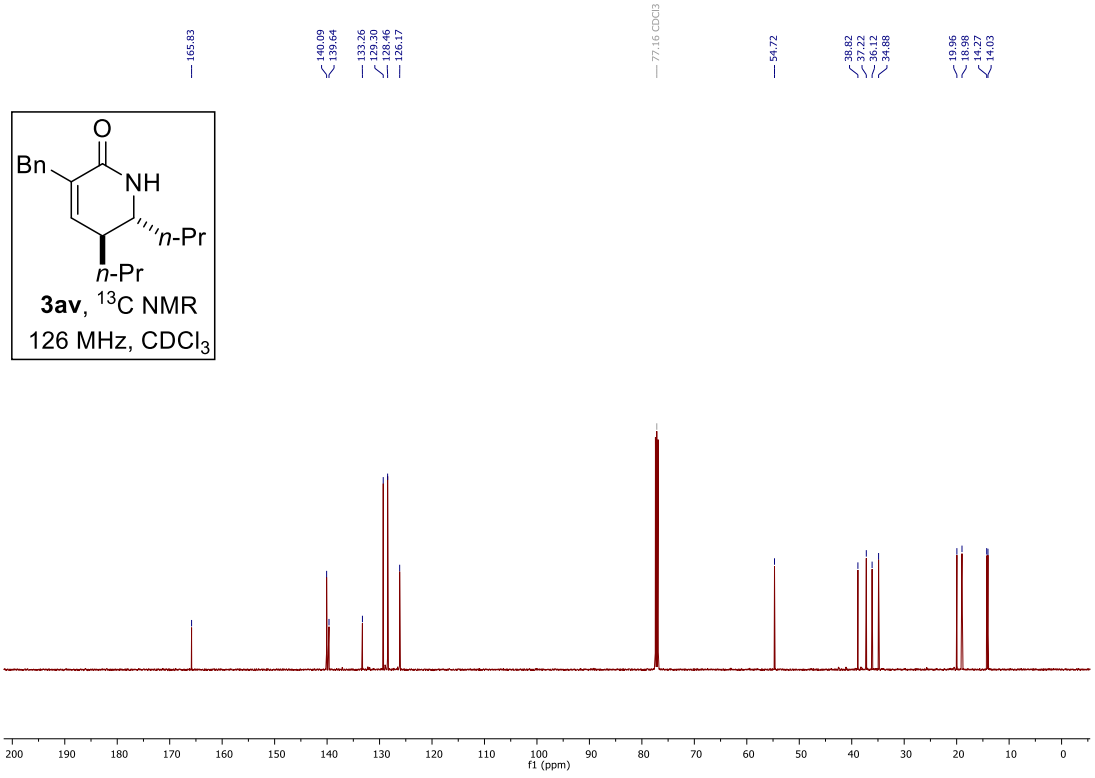


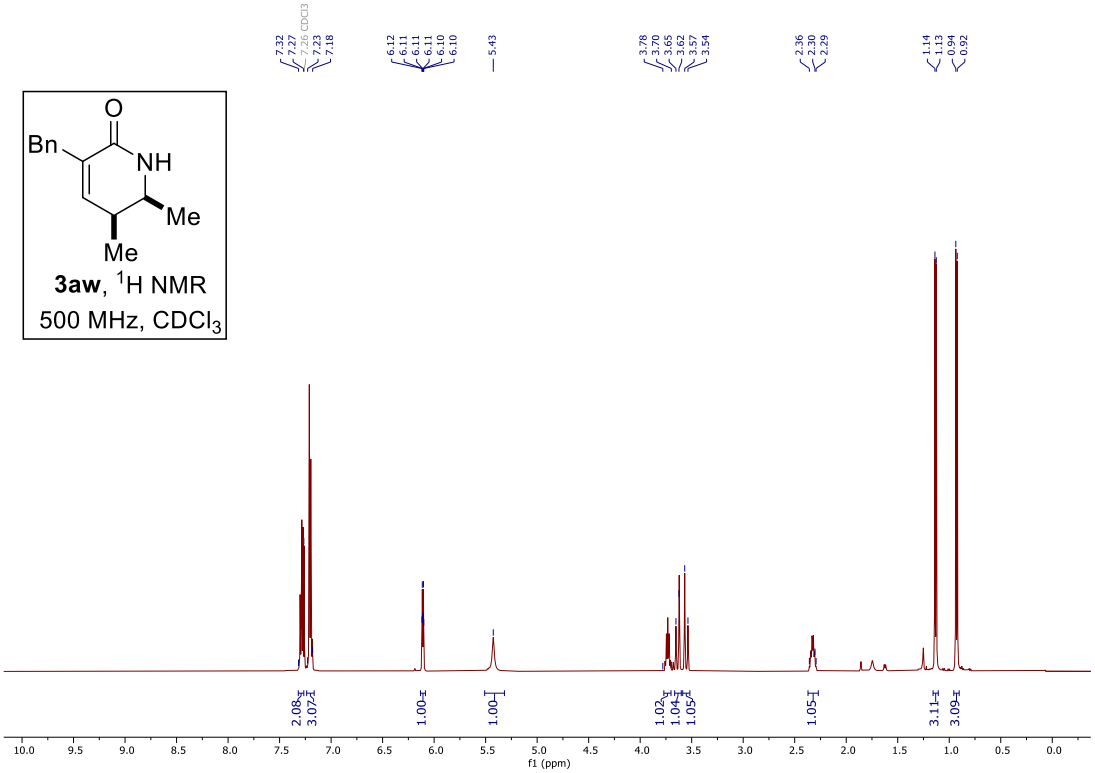


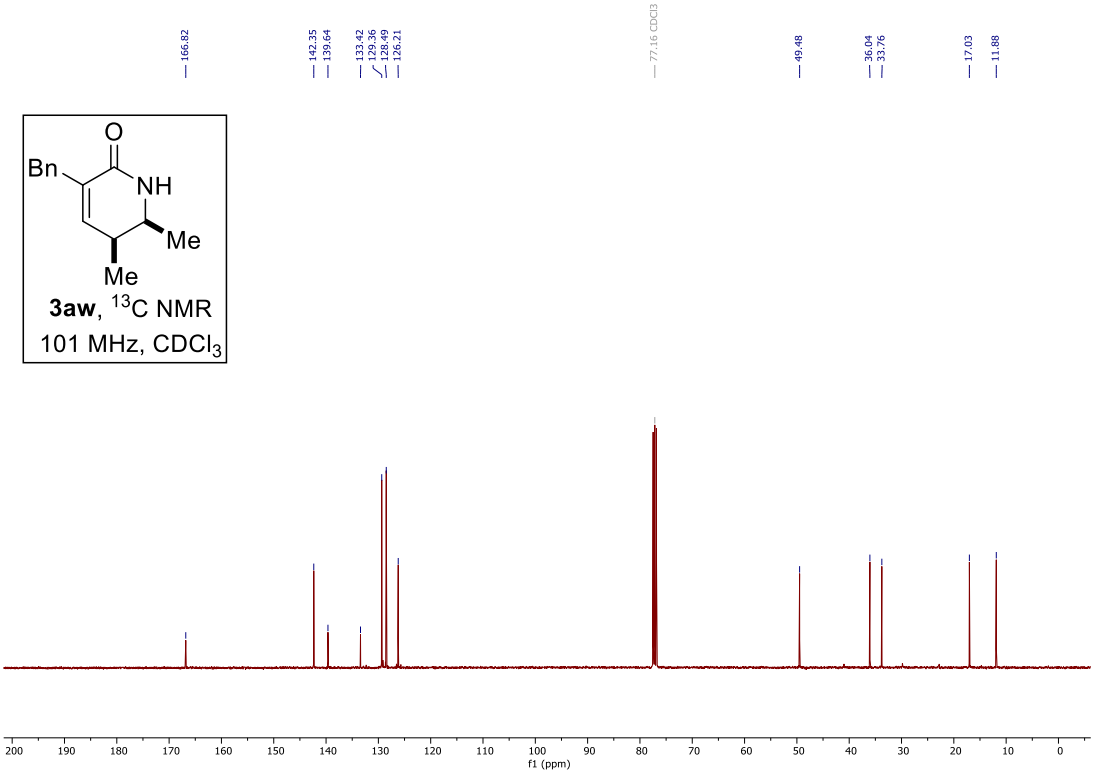
3au, COSY
500 MHz, $CDCl_3$

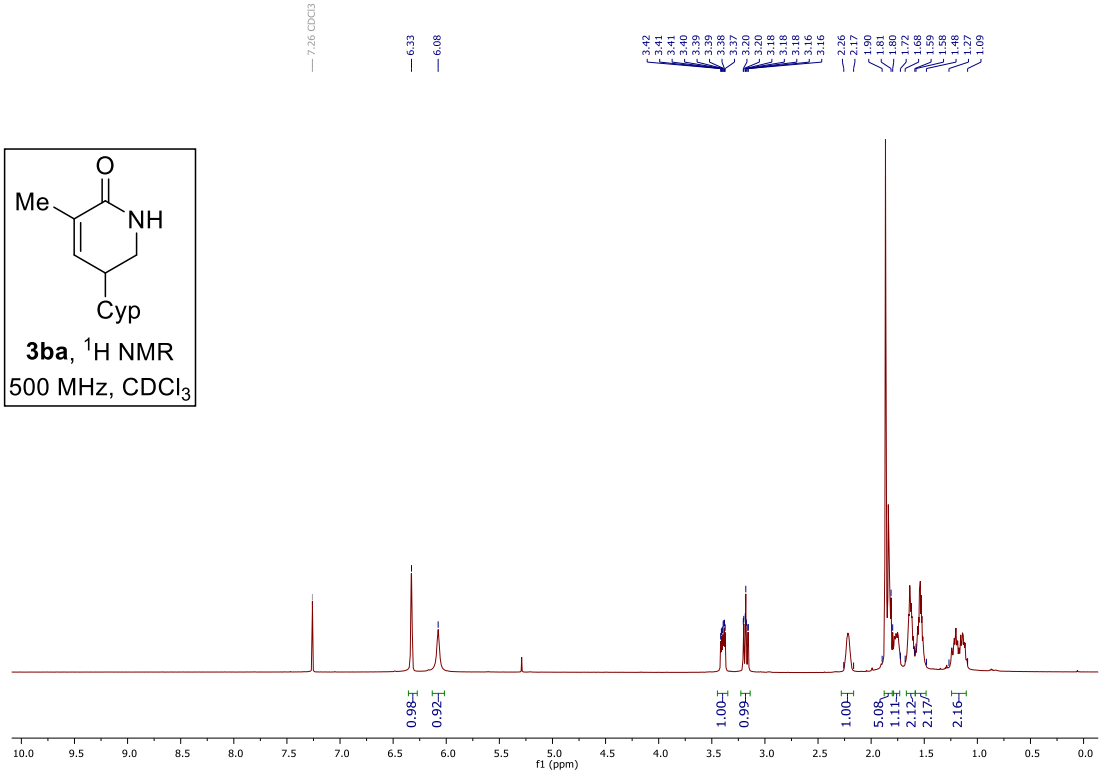


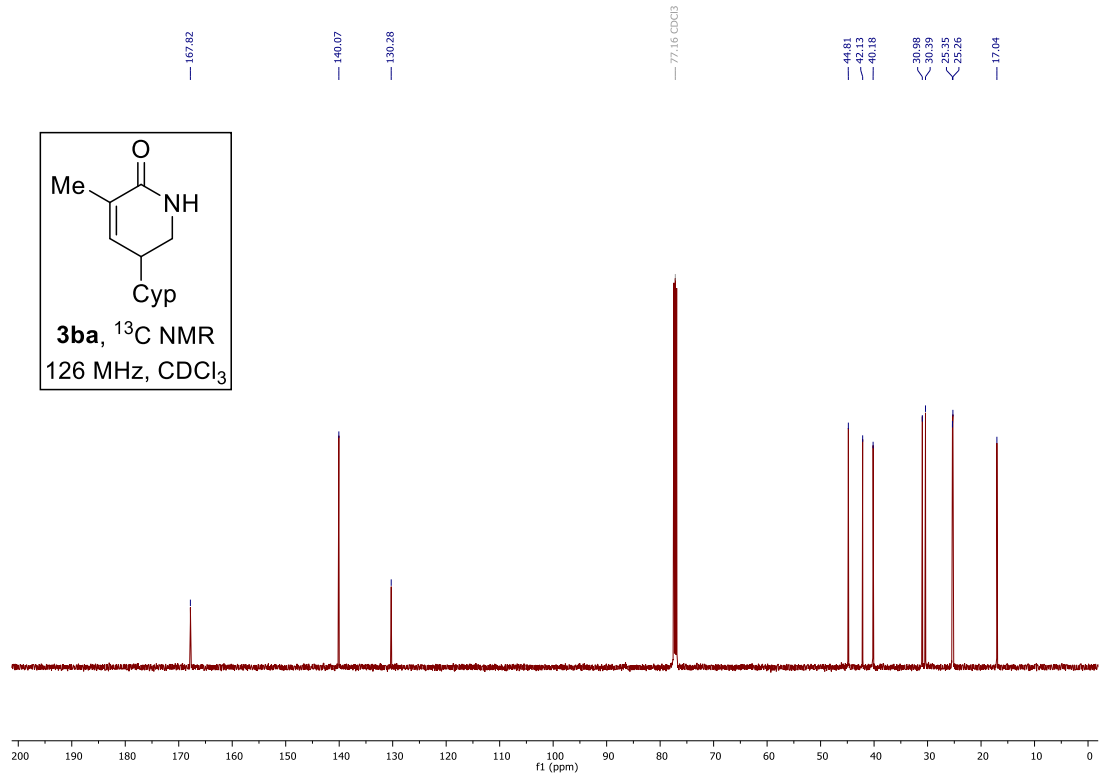

Bn
NH
n-Pr
n-Pr
3av, 1H NMR
500 MHz, CDCl3
f1 (ppm)

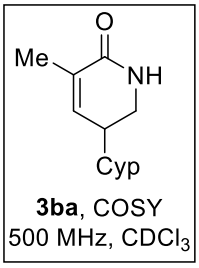

Bn
NH
n-Pr
n-Pr
3av, 13C NMR
126 MHz, CDCl3
f1 (ppm)


Bn
O
NH
Me
Me
3aw, 1H NMR
500 MHz, CDCl3
7.32
7.27
7.26 CDCl3
7.23
7.18
6.12
6.11
6.11
6.11
6.10
6.10
5.43
3.78
3.70
3.65
3.62
3.57
3.54
2.36
2.30
2.29
1.14
1.13
0.94
0.92
2.08
3.07
1.00
1.00
1.02
1.04
1.05
1.05
3.11
3.09
f1 (ppm)

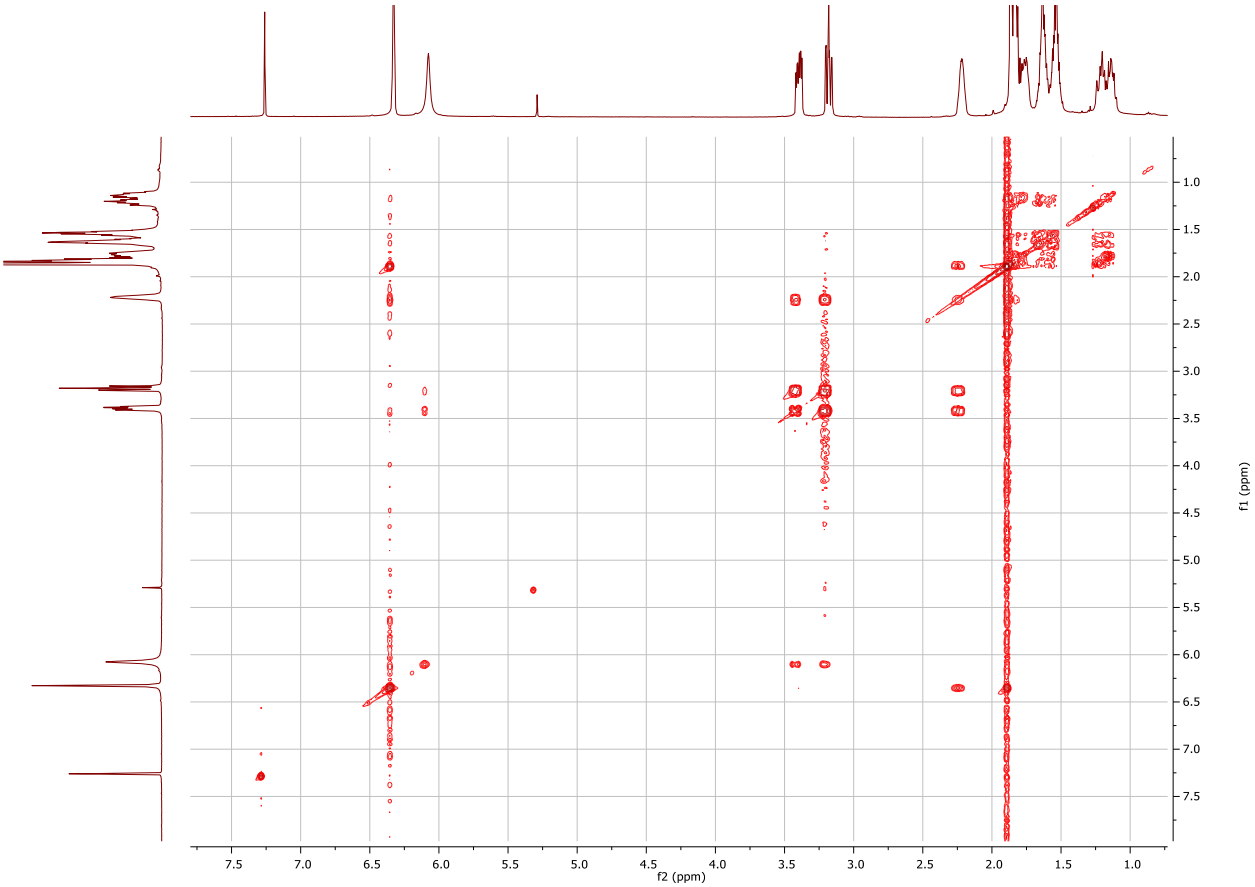

Bn
O
NH
Me
Me
3aw, 13C NMR
101 MHz, CDCl3
166.82
142.35
139.64
133.42
129.36
128.49
126.21
77.16 CDCl3
49.48
36.04
33.76
17.03
11.88
f1 (ppm)

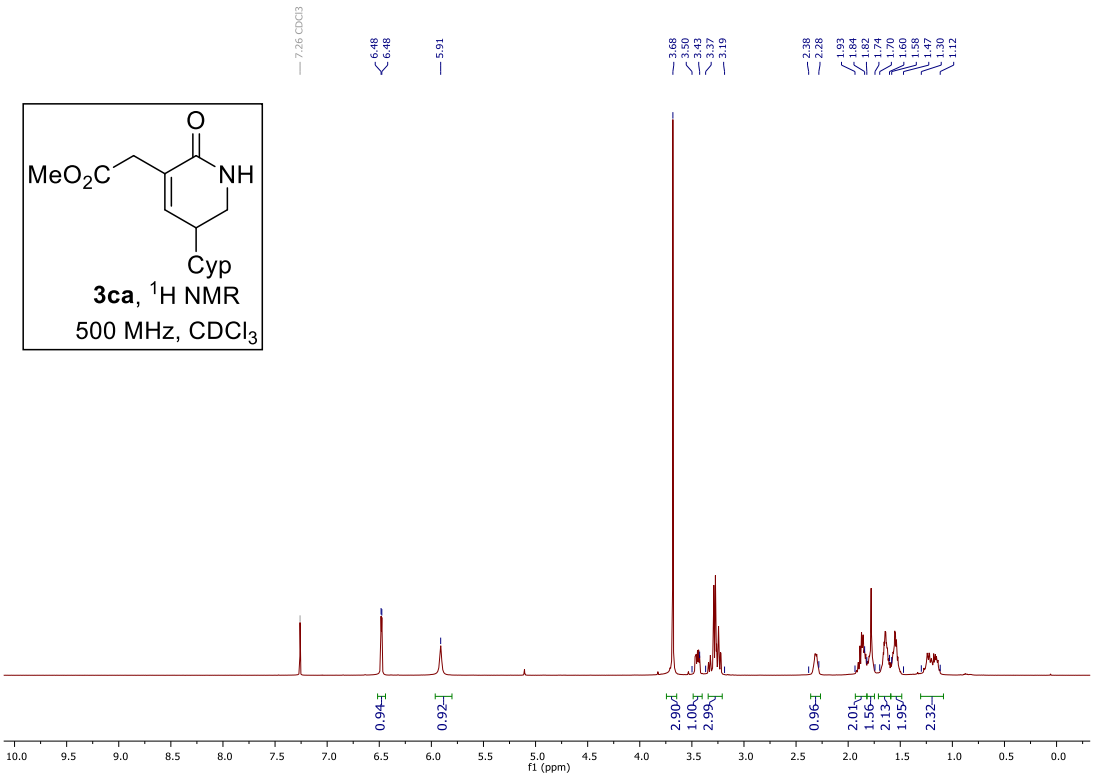

7.26 CDCl3
6.33
6.08
3.42
3.41
3.41
3.40
3.39
3.39
3.38
3.37
3.20
3.20
3.18
3.18
3.18
3.16
3.16
2.26
2.17
1.90
1.81
1.80
1.72
1.68
1.59
1.58
1.48
1.27
1.09
O
Me
NH
Cyp
3ba, 1H NMR
500 MHz, CDCl3
0.98
0.92
1.00
0.99
1.00
5.08
1.11
2.12
2.17
2.16
f1 (ppm)

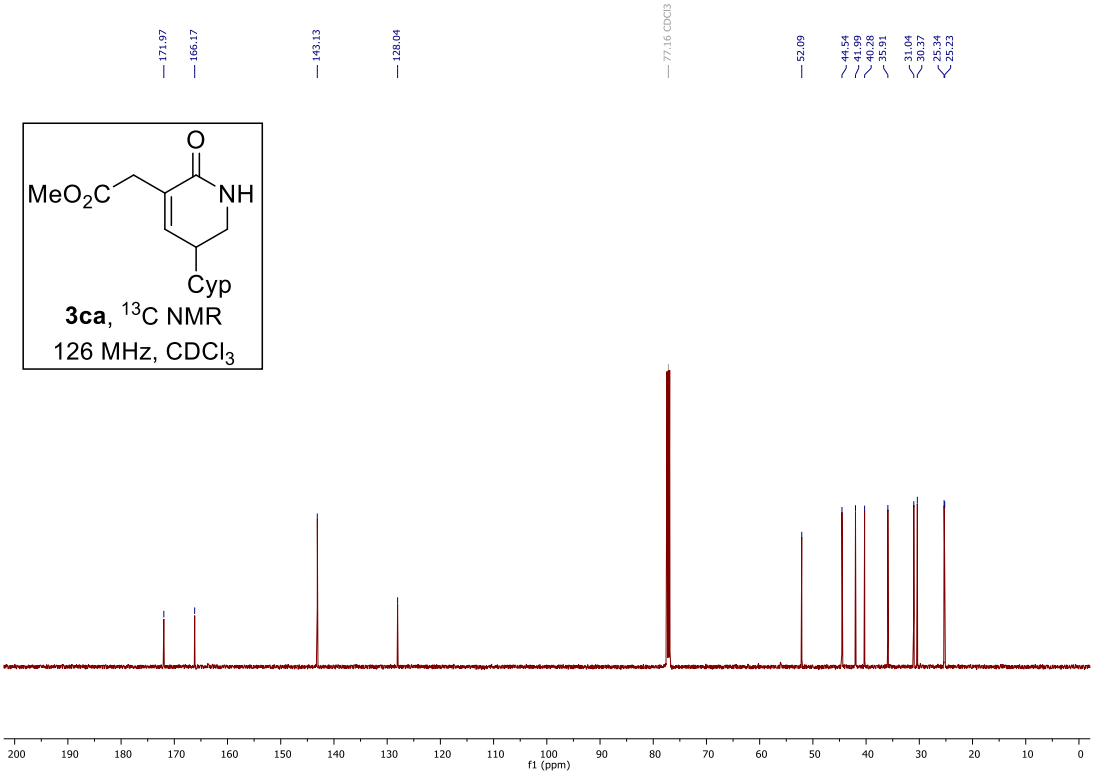

167.82
140.07
130.28
77.16 CDCl3
44.81
42.13
40.18
30.98
30.39
25.35
25.26
17.04
O
Me
NH
Cyp
3ba, 13C NMR
126 MHz, CDCl3
f1 (ppm)

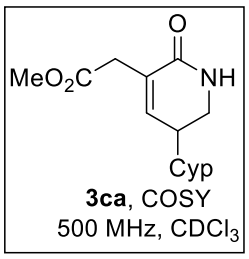


3ba, COSY
500 MHz, $CDCl_3$

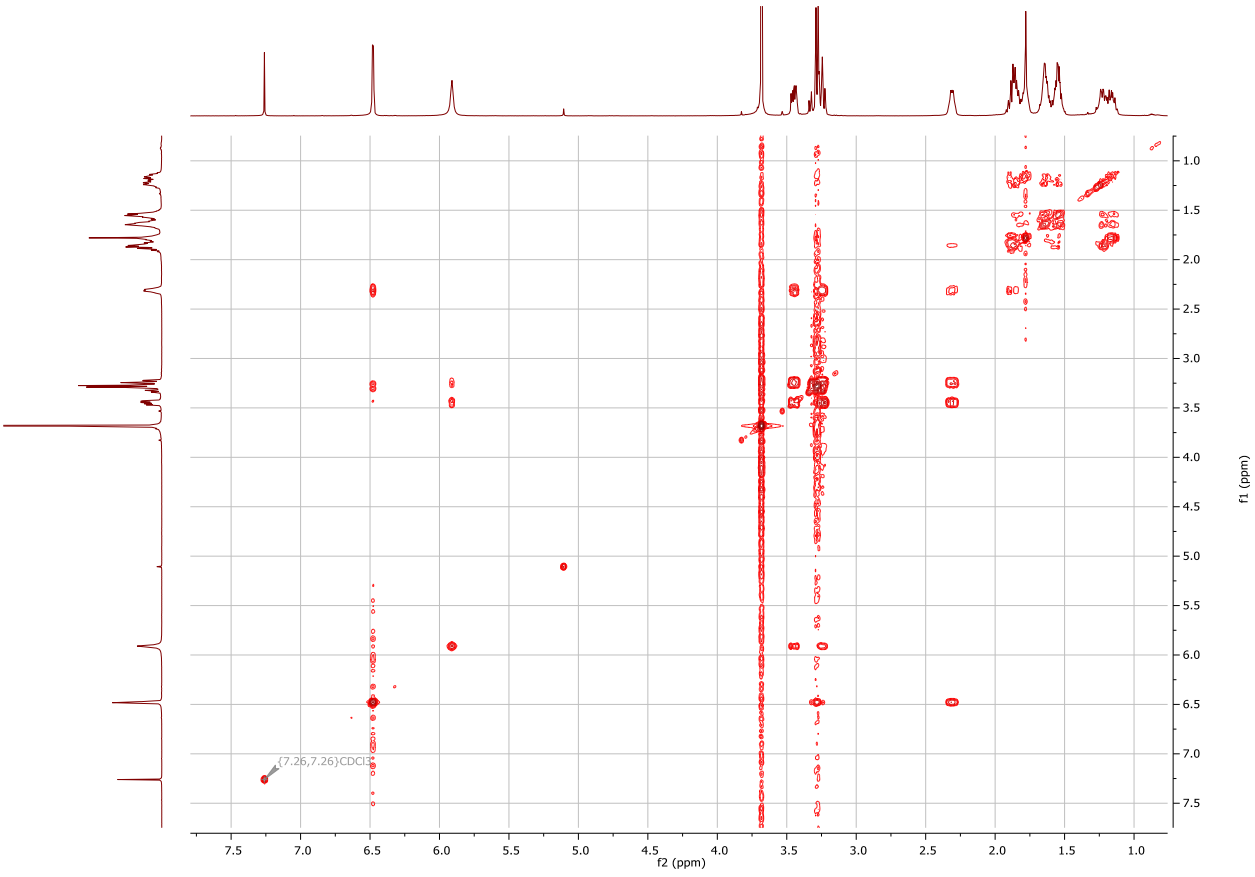


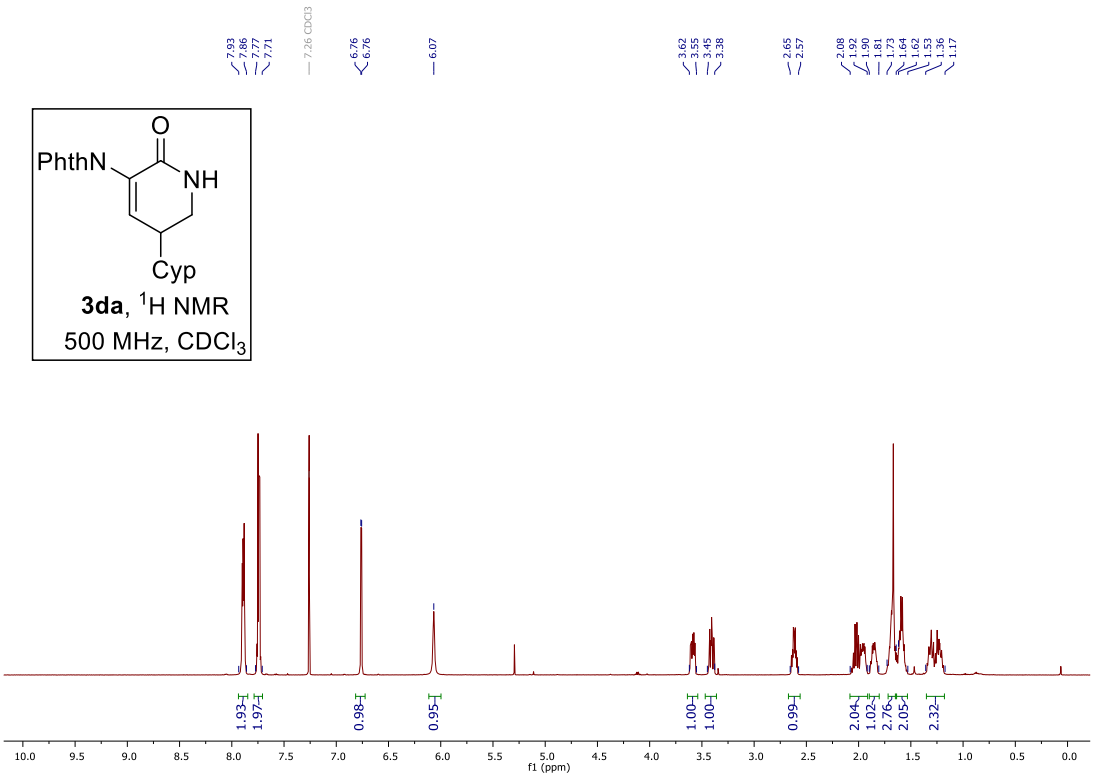

7.26 CDCl3
6.48
6.48
5.91
3.68
3.50
3.43
3.37
3.19
2.38
2.28
1.93
1.84
1.82
1.74
1.70
1.60
1.58
1.47
1.30
1.12
O
MeO2C
NH
Cyp
3ca, 1H NMR
500 MHz, CDCl3
0.94
0.92
2.90
1.00
2.99
0.96
2.01
1.56
2.13
1.95
2.32
f1 (ppm)

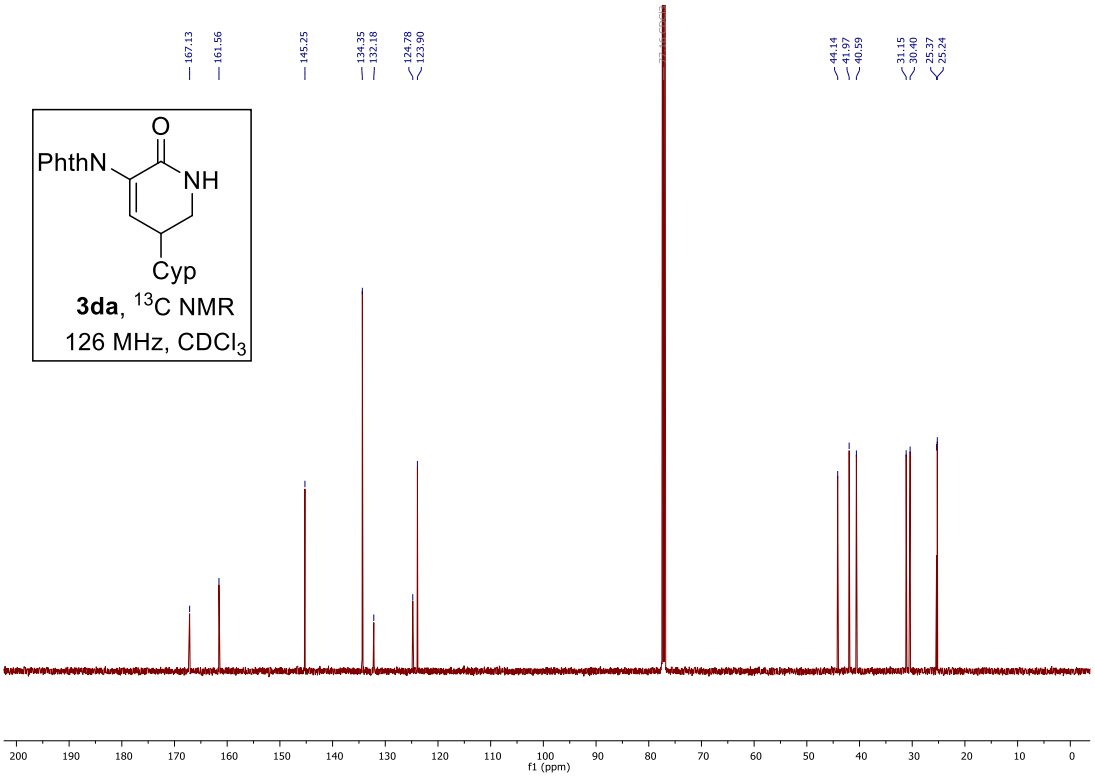

171.97
166.17
143.13
128.04
77.16 CDCl3
52.09
44.54
41.99
40.28
35.91
31.04
30.37
25.34
25.23
O
MeO2C
NH
Cyp
3ca, 13C NMR
126 MHz, CDCl3
f1 (ppm)

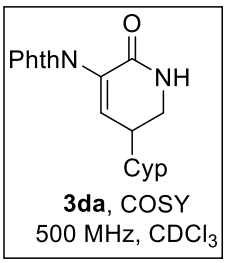


3ca, COSY
500 MHz, $CDCl_3$

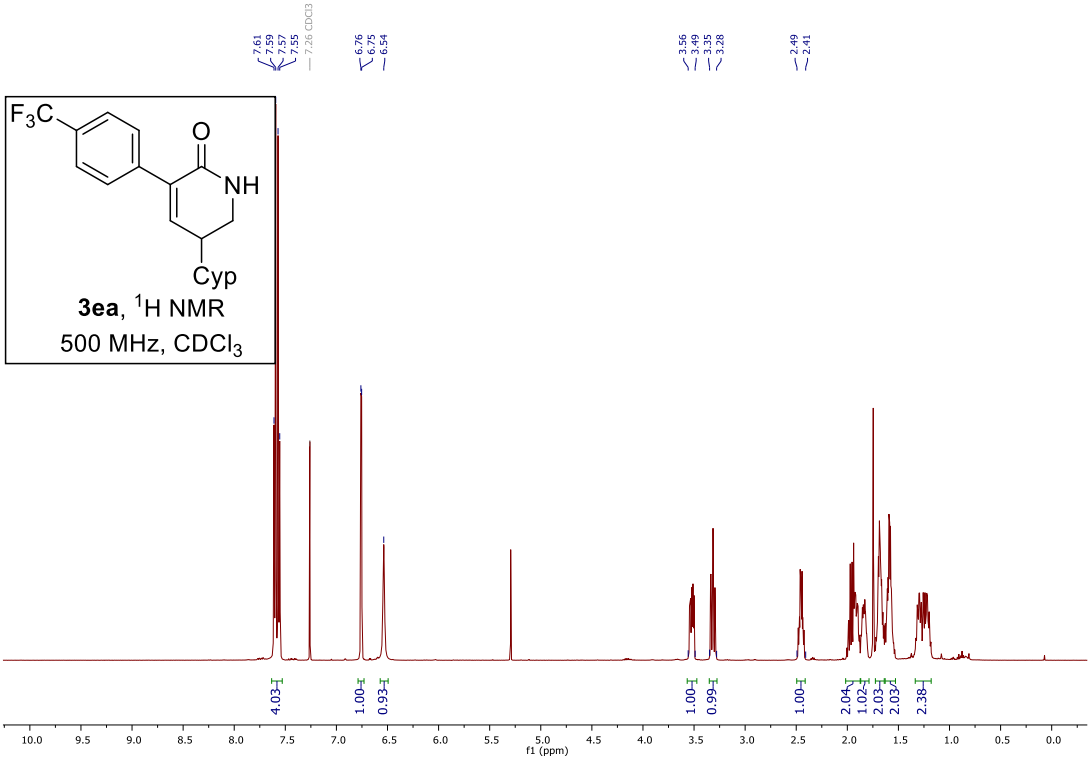


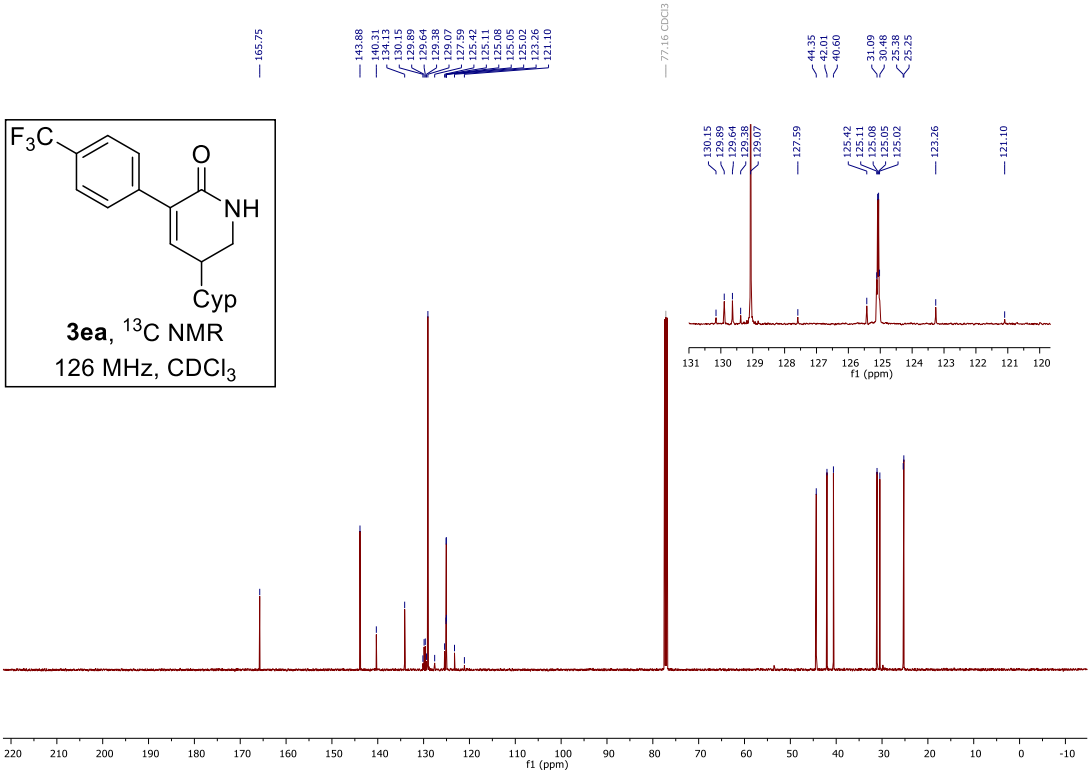

PhthN
O
NH
Cyp
3da, 1H NMR
500 MHz, CDCl3
f1 (ppm)

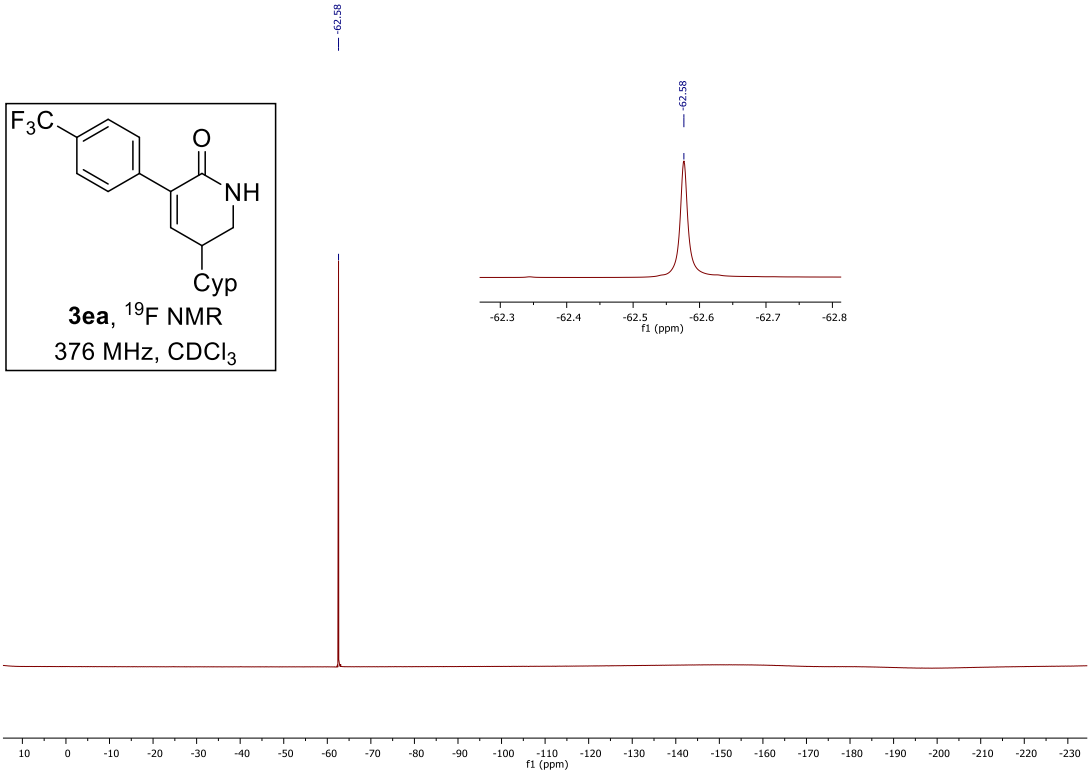

PhthN
O
NH
Cyp
3da, 13C NMR
126 MHz, CDCl3
f1 (ppm)

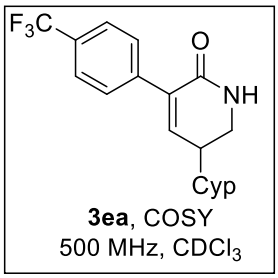


3da, COSY
500 MHz, $CDCl_3$

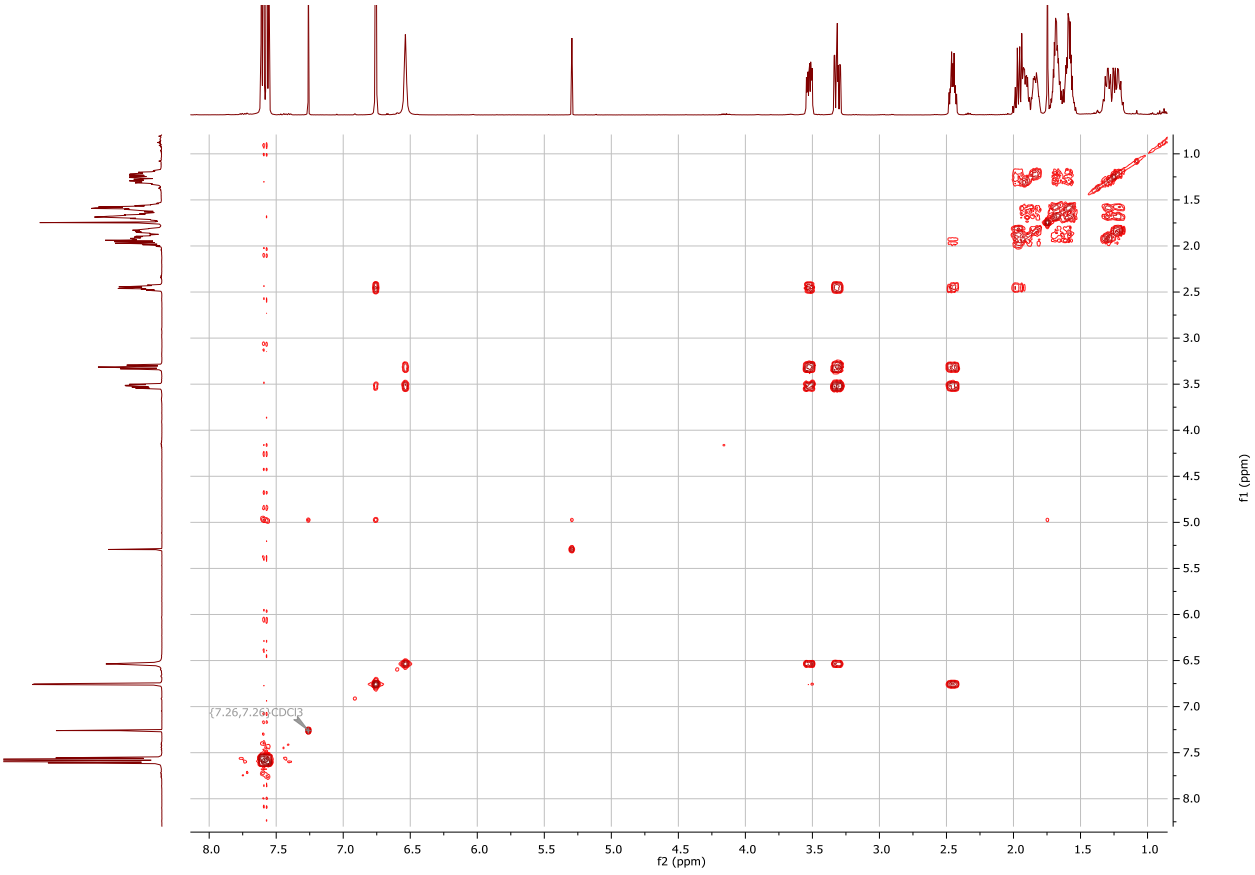

F3C
O
NH
Cyp
3ea, 1H NMR
500 MHz, CDCl3
7.61
7.59
7.57
7.55
7.26 CDCl3
6.76
6.75
6.54
3.56
3.49
3.35
3.28
2.49
2.41
4.03
1.00
0.93
1.00
0.99
1.00
2.04
1.02
2.03
2.03
2.38
f1 (ppm)


F3C
O
NH
Cyp
3ea, 13C NMR
126 MHz, CDCl3
165.75
143.88
140.31
134.13
130.15
129.89
129.64
129.38
129.07
127.59
125.42
125.11
125.08
125.05
125.02
123.26
121.10
77.16 CDCl3
44.35
42.01
40.60
31.09
30.48
25.38
25.25
f1 (ppm)

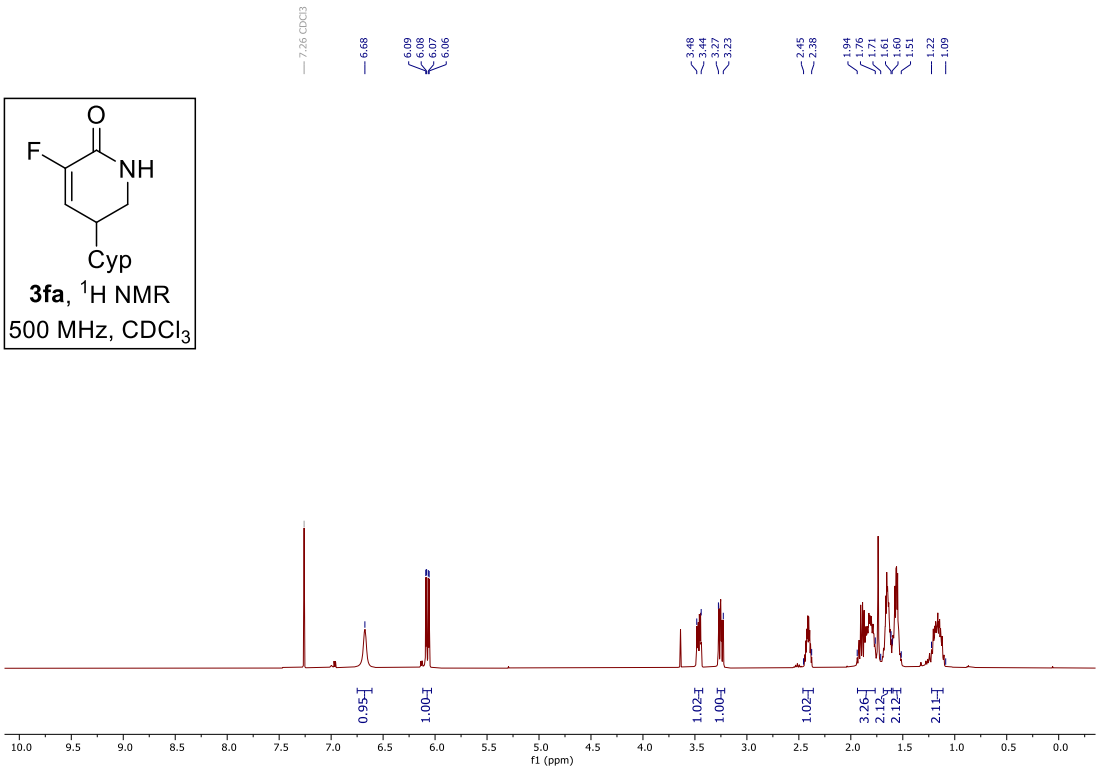

F3C
O
NH
Cyp
3ea, 19F NMR
376 MHz, CDCl3
-62.58
-62.58
-62.3
-62.4
-62.5
-62.6
-62.7
-62.8
f1 (ppm)
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
f1 (ppm)



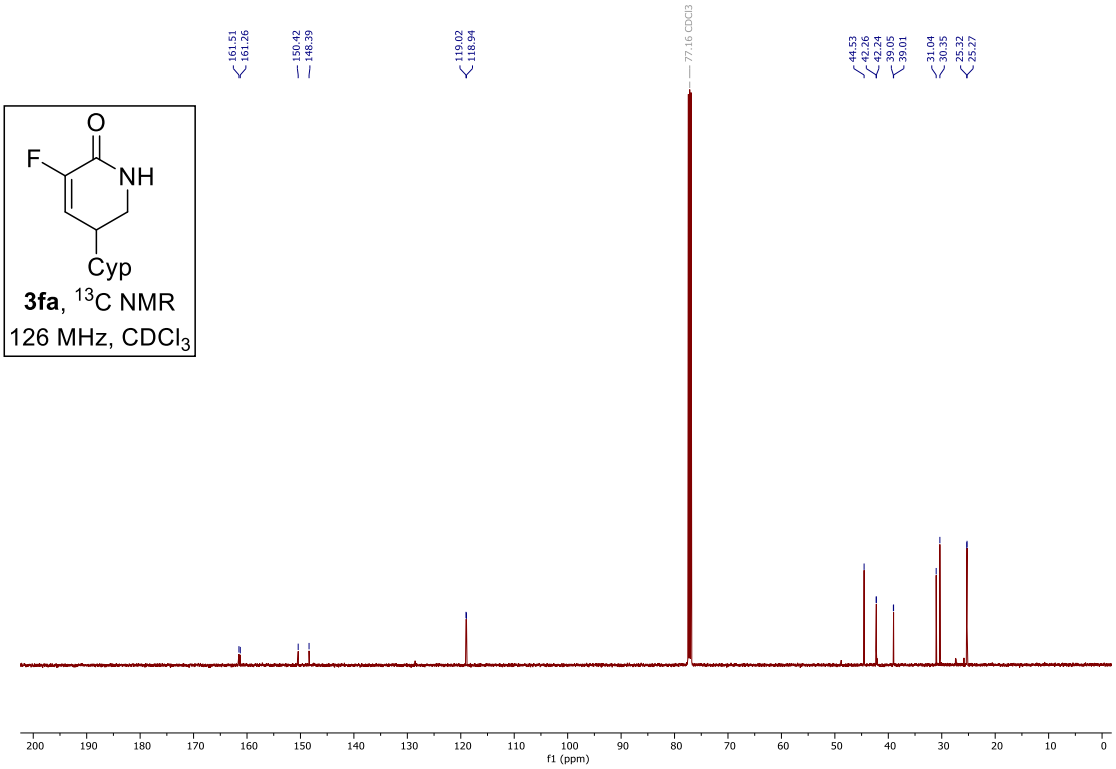
3ea, COSY
500 MHz, $CDCl_3$

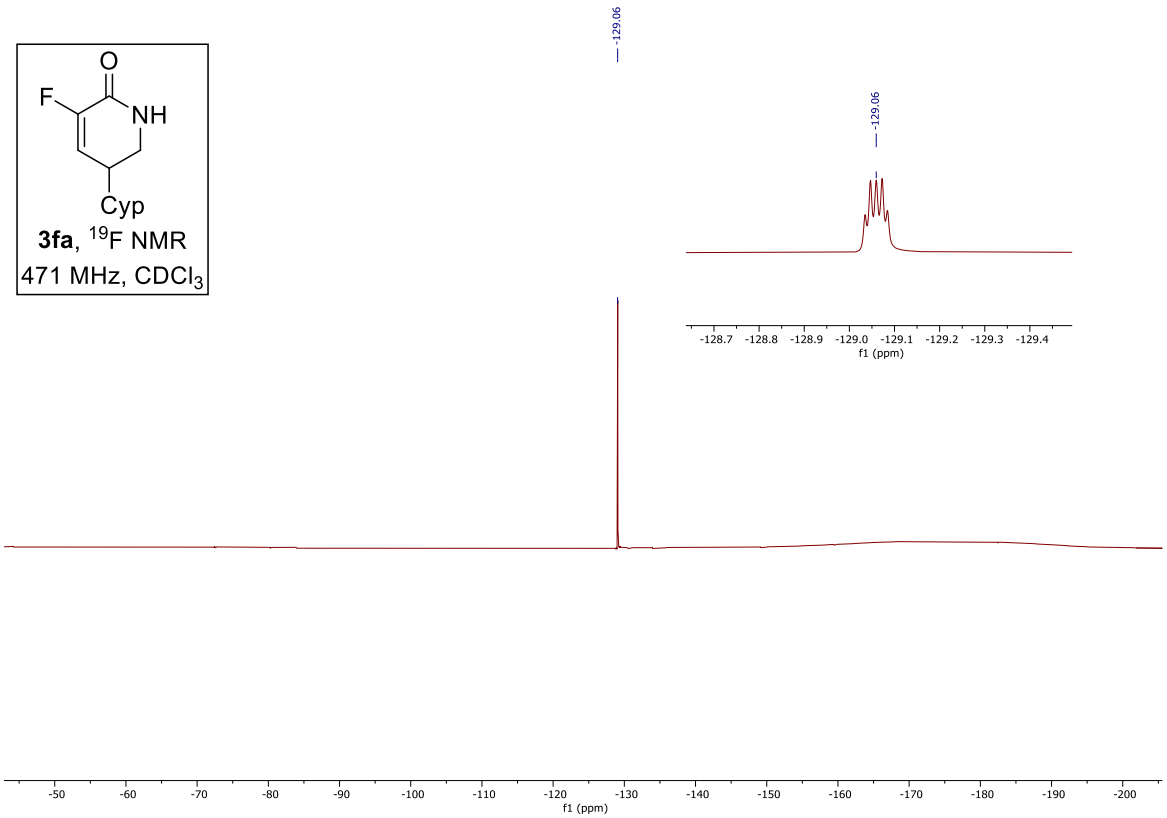


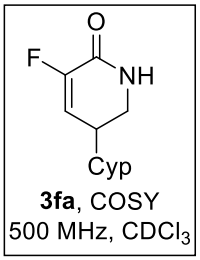
3fa, ^{1}H NMR
500 MHz, $CDCl_3$



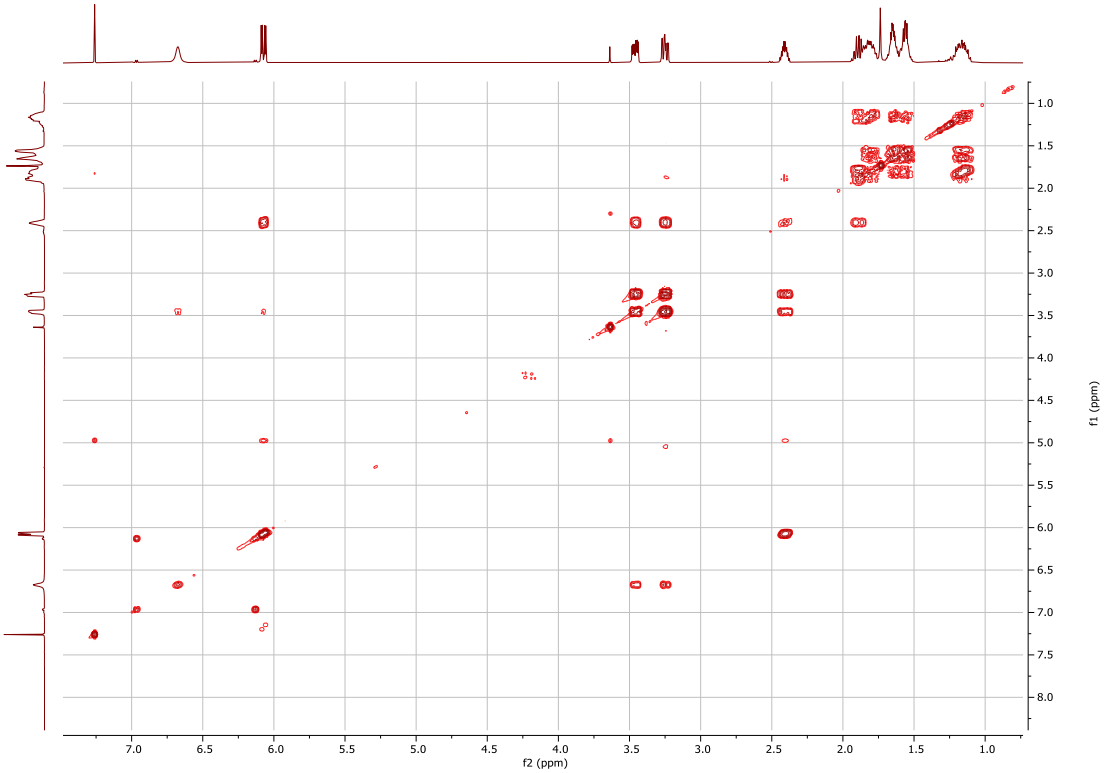
3fa, ^{13}C NMR
126 MHz, $CDCl_3$

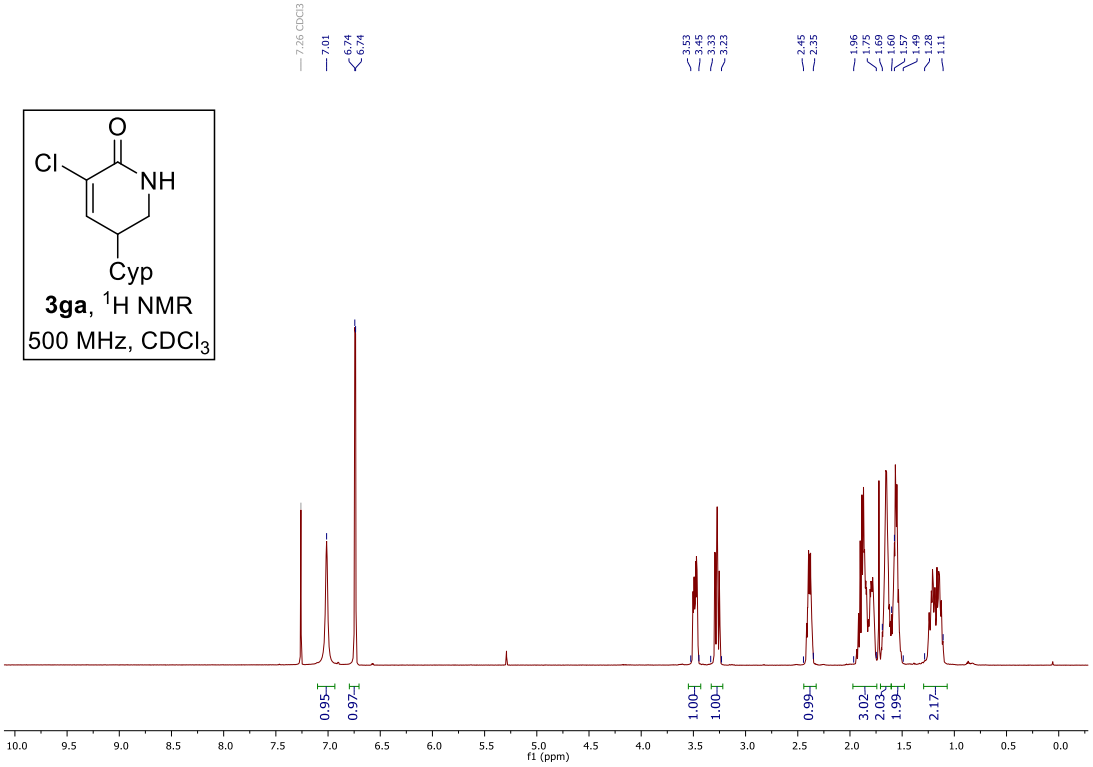


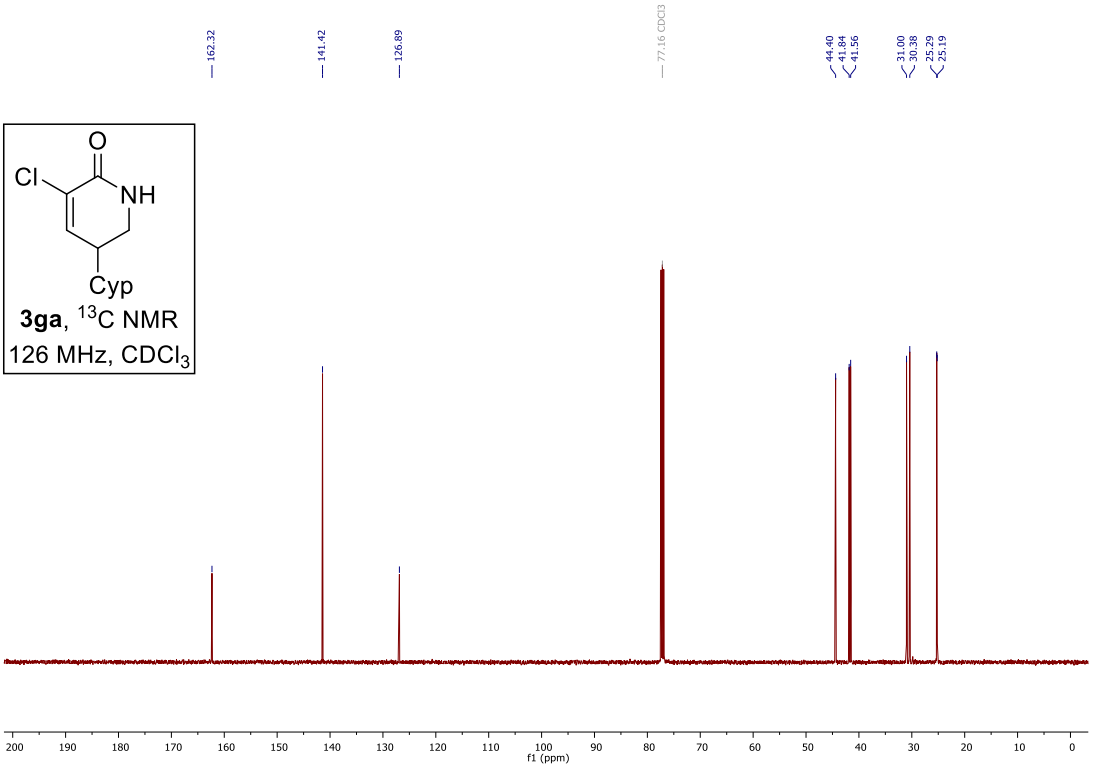

O
F
NH
Cyp
3fa, 19F NMR
471 MHz, CDCl3
-129.06
-129.06
-128.7 -128.8 -128.9 -129.0 -129.1 -129.2 -129.3 -129.4
f1 (ppm)
-50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

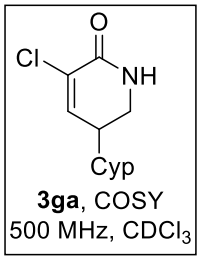


3fa, COSY
500 MHz, $CDCl_3$

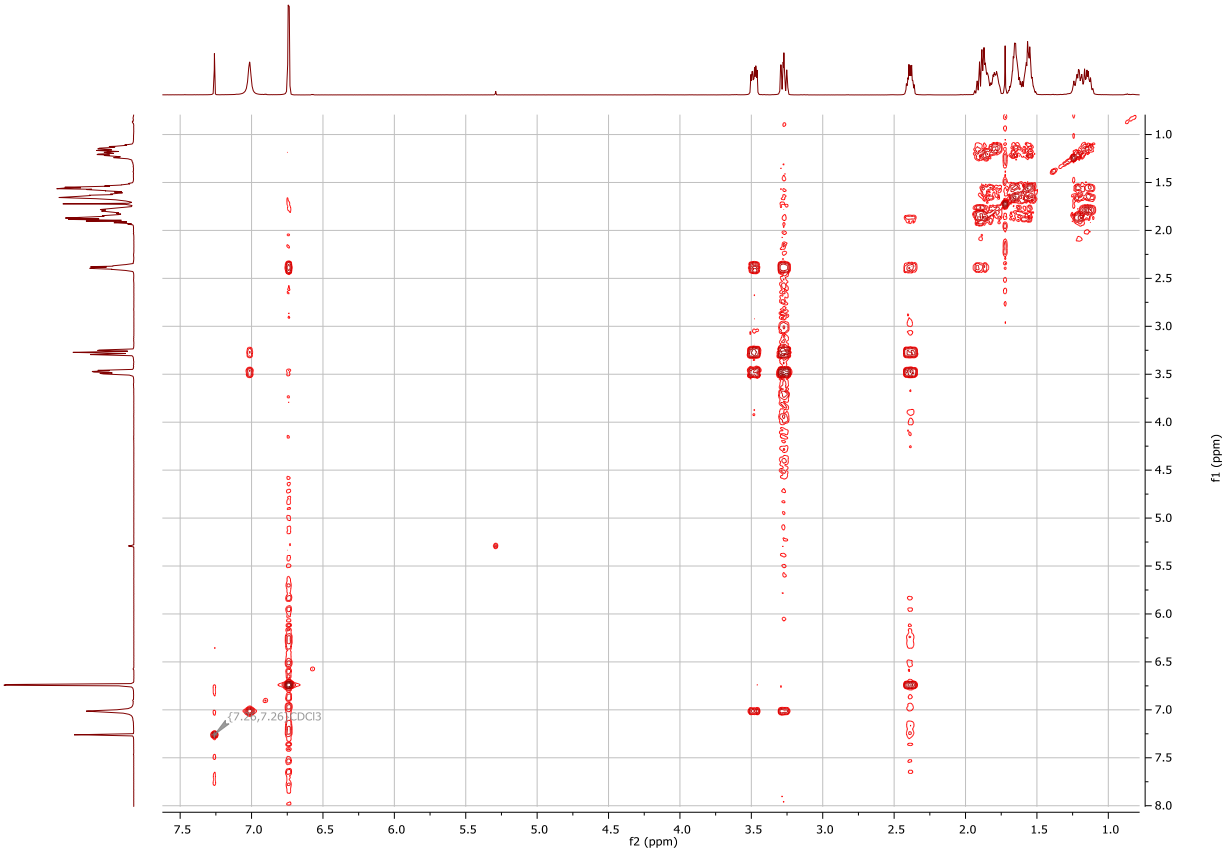


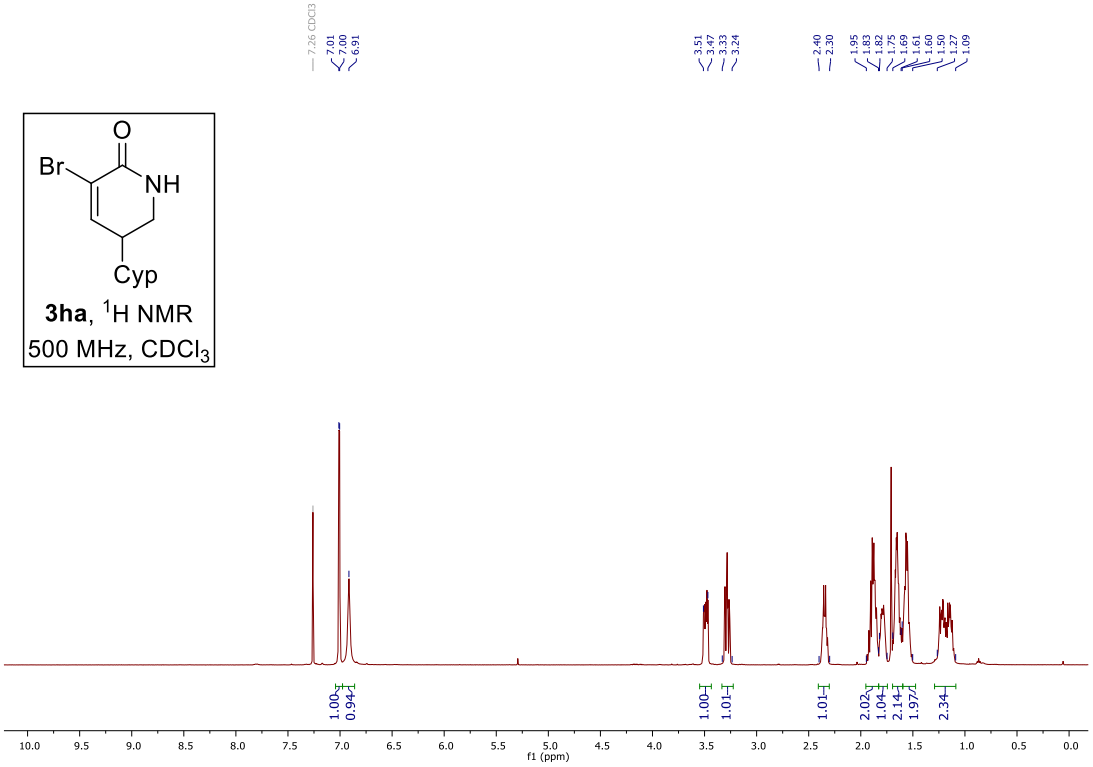

7.26 CDCl3
7.01
6.74
6.74
3.53
3.45
3.33
3.23
2.45
2.35
1.96
1.75
1.69
1.60
1.57
1.49
1.28
1.11
O
Cl
NH
Cyp
3ga, 1H NMR
500 MHz, CDCl3
0.95
0.97
1.00
1.00
0.99
3.02
2.03
1.99
2.17
f1 (ppm)

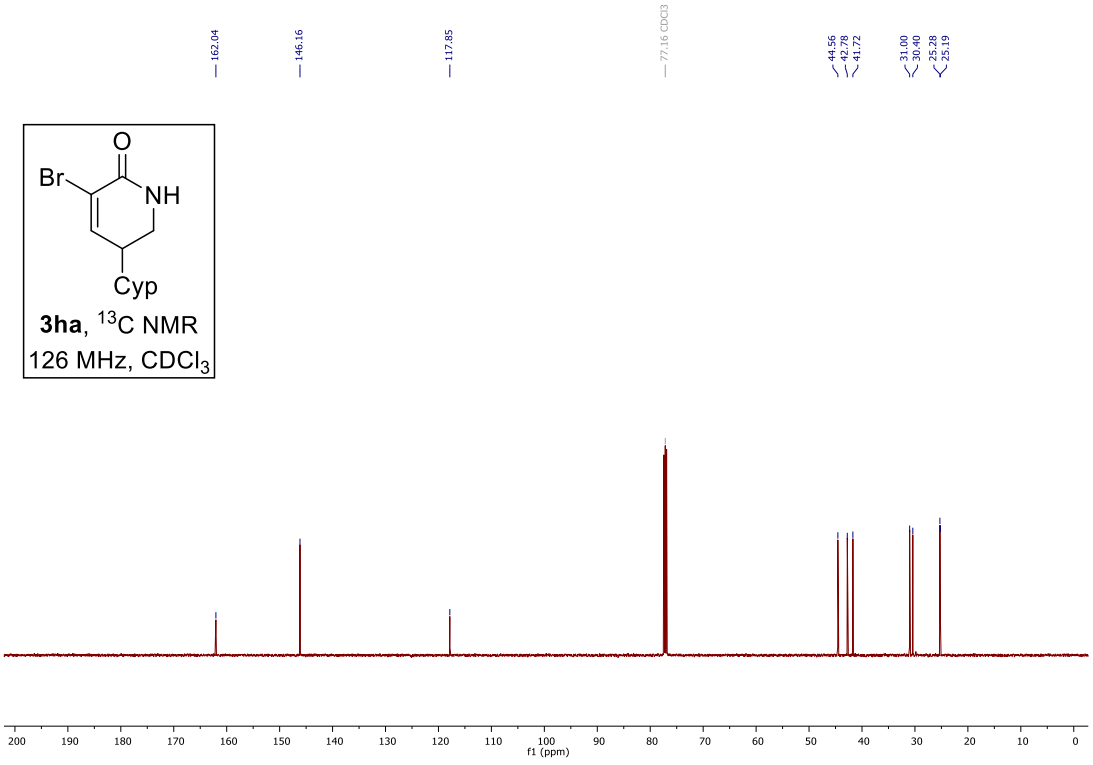

162.32
141.42
126.89
77.16 CDCl3
44.40
41.84
41.56
31.00
30.38
25.29
25.19
O
Cl
NH
Cyp
3ga, 13C NMR
126 MHz, CDCl3
f1 (ppm)

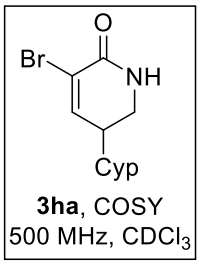


3ga, COSY
500 MHz, $CDCl_3$

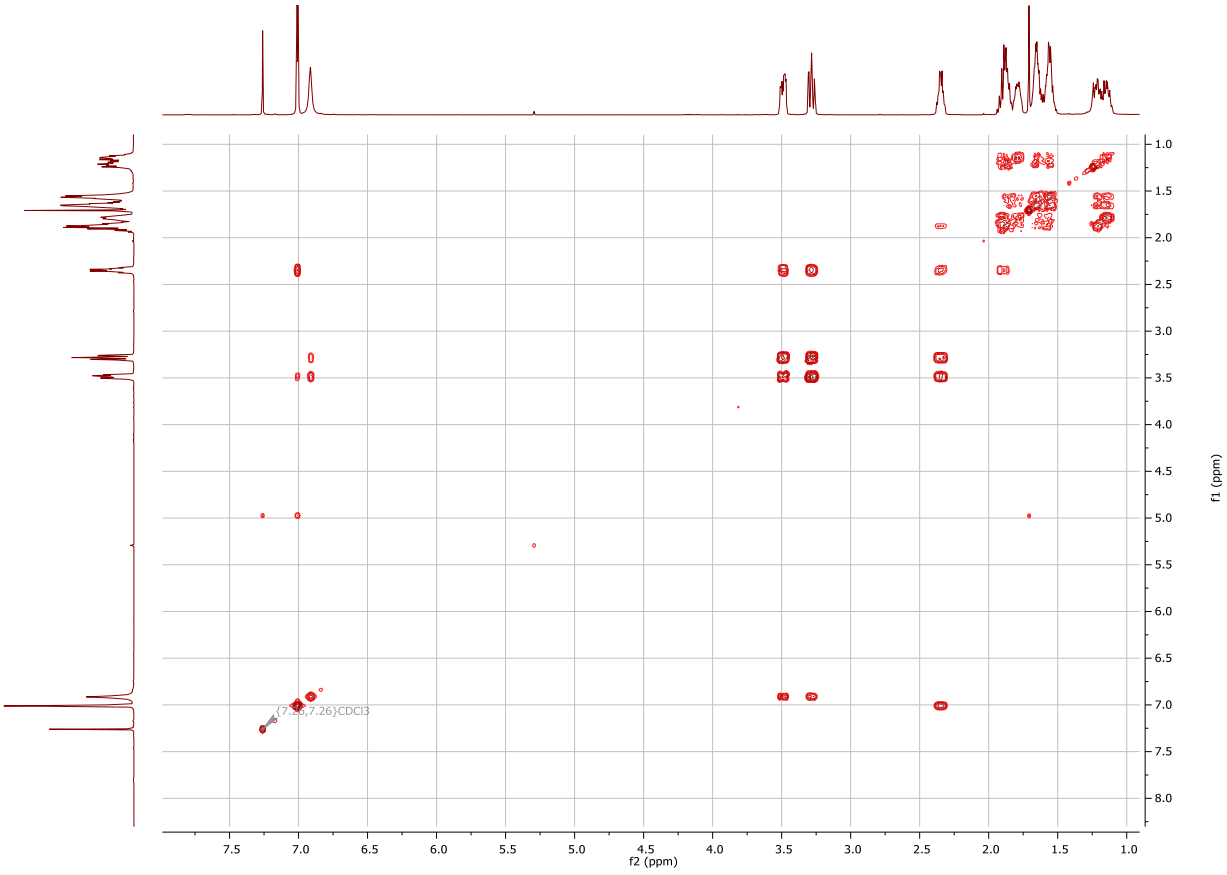


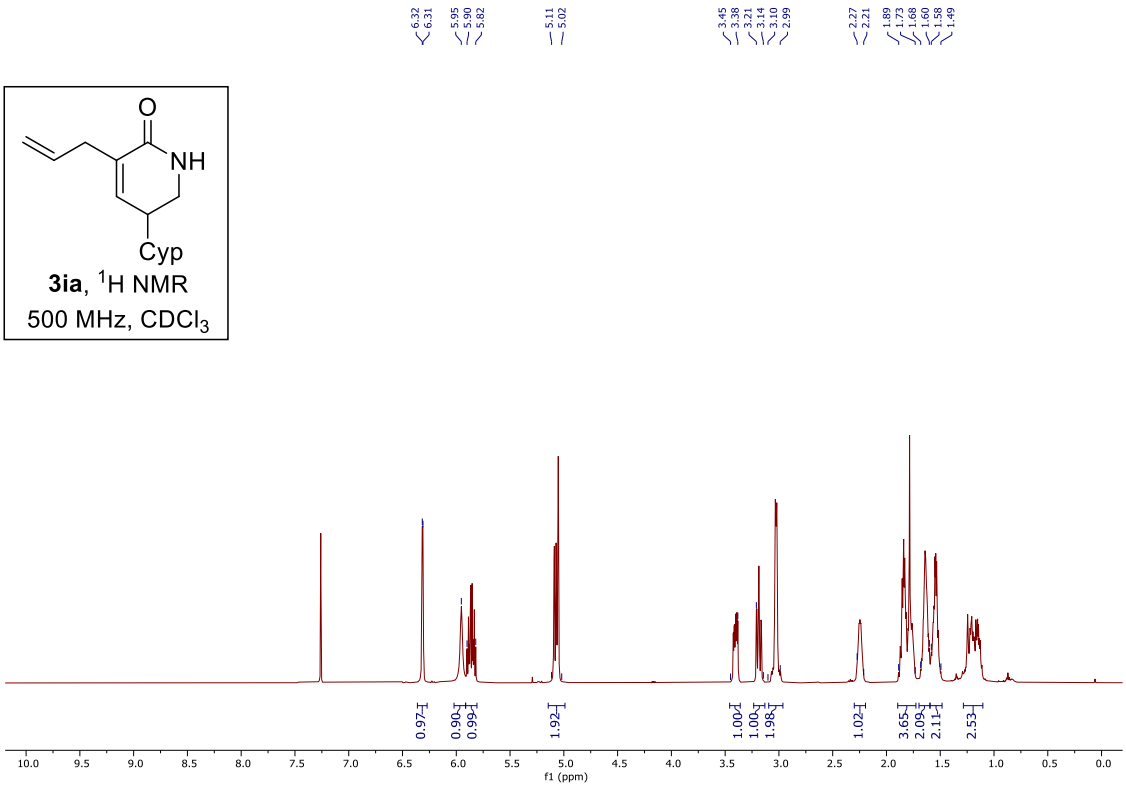

7.26 CDCl3
7.01
7.00
6.91
3.51
3.47
3.33
3.24
2.40
2.30
1.95
1.83
1.82
1.75
1.69
1.61
1.60
1.50
1.27
1.09
O
Br
NH
Cyp
3ha, 1H NMR
500 MHz, CDCl3
1.00
0.94
1.00
1.01
1.01
2.02
1.04
2.14
1.97
2.34
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

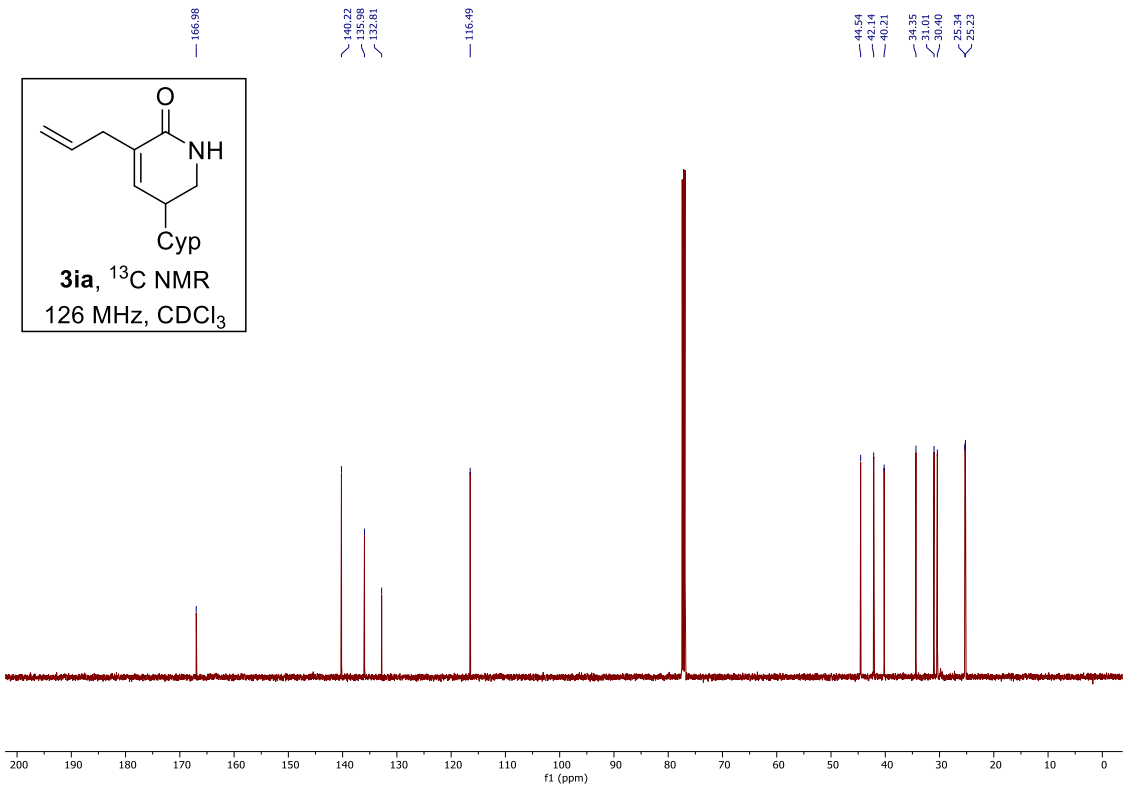

162.04
146.16
117.85
77.16 CDCl3
44.56
42.78
41.72
31.00
30.40
25.28
25.19
O
Br
NH
Cyp
3ha, 13C NMR
126 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

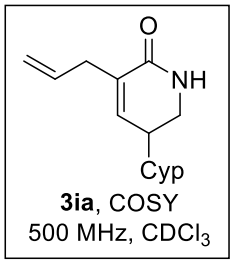


3ha, COSY
500 MHz, $CDCl_3$

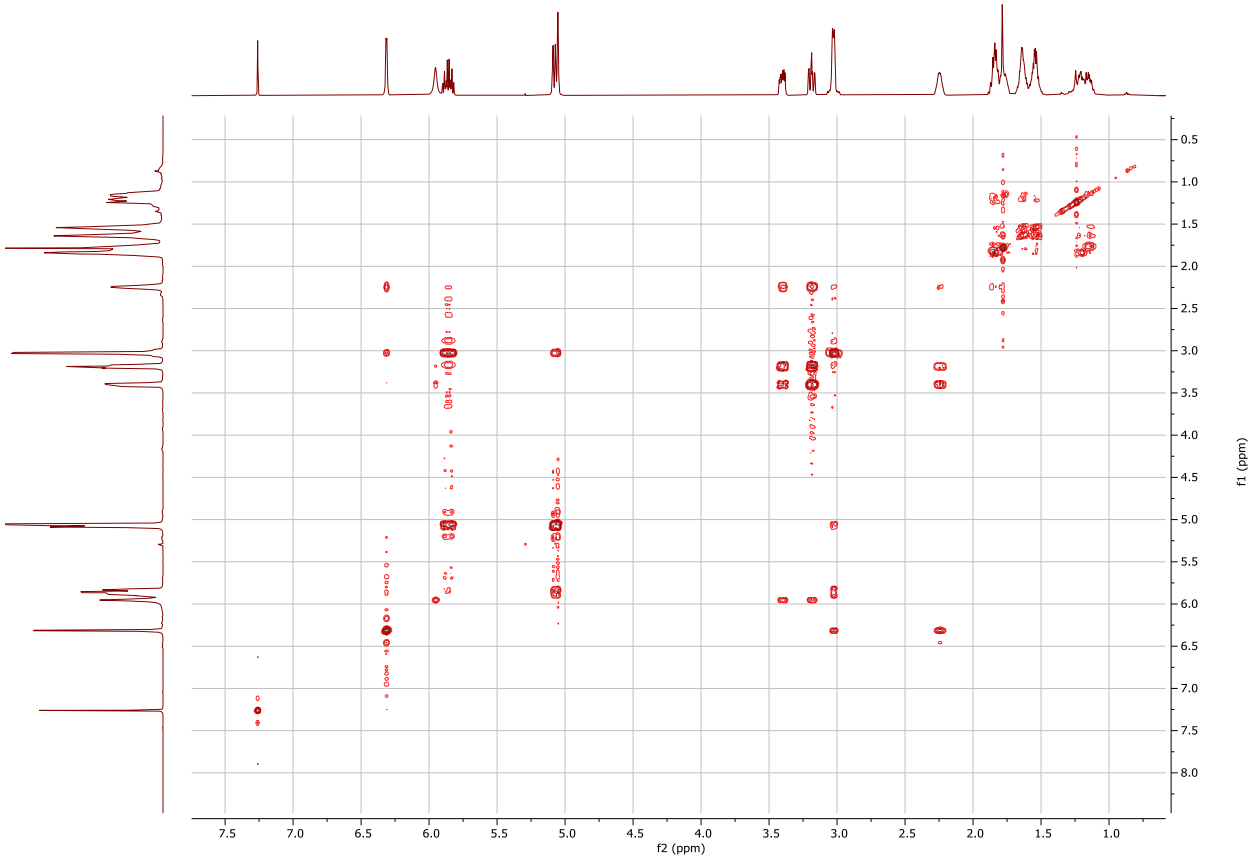



6.32
6.31
5.95
5.90
5.82
5.11
5.02
3.45
3.38
3.21
3.14
3.10
2.99
2.27
2.21
1.89
1.73
1.68
1.60
1.58
1.49
O
NH
Cyp
3ia, 1H NMR
500 MHz, CDCl3
0.97
0.90
0.99
1.92
1.00
1.00
1.98
1.02
3.65
2.09
2.11
2.53
f1 (ppm)


166.98
140.22
135.98
132.81
116.49
44.54
42.14
40.21
34.35
31.01
30.40
25.34
25.23
O
NH
Cyp
3ia, 13C NMR
126 MHz, CDCl3
f1 (ppm)



3ia, COSY
500 MHz, $CDCl_3$



Appendix C

SUPPLEMENTARY DATA FOR CHAPTER FOUR

Supporting Information

Rh(III)-Catalyzed Three-Component *syn*-Carboamination of Alkenes Using Arylboronic Acids and Dioxazolones

Sumin Lee and Tomislav Rovis*

Department of Chemistry, Columbia University, New York, New York 10027

Contents

1. General information

All reactions were carried out using oven-dried glassware with magnetic stirring unless otherwise noted. Anhydrous solvents and reagents were purchased from commercial sources and used without further purification. Flash chromatography was conducted either manually on SiliCycle® SilicaFlash® P60 (230-400 mesh) silica gel, SiliCycle® prep TLC (TLG-R10011B-341, thickness 1000um) or automatically *via* a Teledyne Isco Lumen CombiFlash with RediSep Rf Disposable Flash columns. Thin layer chromatography (TLC) was performed on Silicycle 250μm silica gel 60 Å plates. Visualization was accomplished with UV light (254 nm) and $KMnO_4$. ^1H, ^{19}F NMR, and ^{13}C NMR spectra were collected at ambient temperature on Bruker 400 MHz or Bruker Avance III 500 MHz spectrometers unless otherwise noted. Chemical shifts (δ) are reported in parts per million (ppm), coupling constants (J) are reported in Hz, and multiplicity is described using the following abbreviations: singlet (s), broad (b), multiplet (m), doublet (d), triplet (t), quartet (q), or combinations thereof. ^1H NMR spectra were referenced to 7.26 ppm ($CHCl_3$) or 0.0 ppm (TMS). ^{13}C NMR spectra were referenced to 77.16 ppm ($CDCl_3$) and all peaks given are singlet unless otherwise noted. Diastereomeric and regioisomeric ratios were measured by integration of ^1H NMR spectra of product mixtures prior to purification. High resolution mass spectra (HRMS) were obtained from Columbia University Mass Spectrometry Facility on a JOEL JMSHX110HF mass spectrometer using the ASAP ionization model. Infrared spectra were collected on a Perkin Elmer Spectrum Two FT-IR Spectrometer.

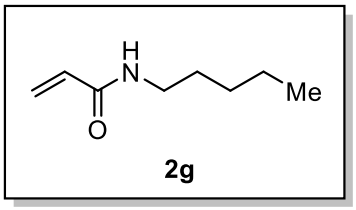
2. Preparation of starting materials

All boronic acids (**1a**-**1r**), alkenes **2b**, **2c**, **2d**, **2e**, and **2i** were purchased from commercial sources and used without purification. Alkene **2f**,[1] **2j**,[2] **2k**,[3] **2l**[4], **2m**[5] and dioxazolone **3c**,[6] **3d**,[7] **3e**,[8] **3f**,[7] **3g**,[6] and **3h**[7] were synthesized following literatures. Alkenes **2g**, **2h**, and dioxazolone **3b** were synthesized following the procedures below.

General procedure A: the synthesis of acrylamides (2g-2h)

To a solution of primary amine (or corresponding HCl salt, 1 equiv) and triethylamine (1.1 equiv) in dichloromethane (0.5 M) was added acryloyl chloride (1.1 equiv) in dichloromethane at 0 °C. The mixture was stirred at 0 °C for 15 minutes and warmed to room temperature. The reaction was stirred at room temperature for 3 hours. The volatiles was removed by a rotary evaporator then ethyl acetate was added

and filtered through celite. The filtrate was washed with 1M HCl, saturated $NaHCO_3$ solution, and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate) to afford the corresponding acrylamides.



2g

Yield: Prepared according to general procedure **A** from 1-aminopentane (10 mmol). 78%, 1.11g, colorless oil.

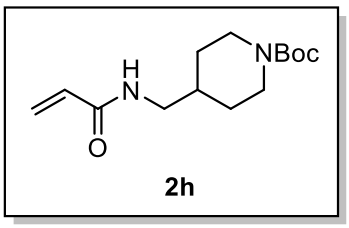
$\mathbf{R_f}$ = 0.39 (EA/Hex 2:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (d, J = 17.1 Hz, 1H), 6.11 (dd, J = 17.0, 10.2 Hz, 1H), 6.05 (s, 1H), 5.58 (dt, J = 10.0 Hz, 1H), 3.28 (q, J = 7.3, 6.7 Hz, 2H), 1.50 (q, J = 7.2 Hz, 2H), 1.36 – 1.21 (m, 4H), 0.87 (t, J = 6.8, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.75, 131.22, 125.99, 39.70, 29.33, 29.18, 22.43, 14.04.

IR ($CDCl_3$, cm^{-1}) ν 3276, 3079, 2957, 2929, 2861, 1656, 1623, 1548, 1407, 1245, 985, 954, 727.

HRMS (ASAP) m/z $[C_8H_{16}NO]^+$ ($[M+H]^+$) calculated 142.1232, found 142.1236.



2h

Yield: Prepared according to general procedure **A** from 1-Boc-4-(aminomethyl)piperidine (10 mmol). 65%, 1.74g, colorless oil.

$\mathbf{R_f}$ = 0.18 (EA/Hex 2:3).

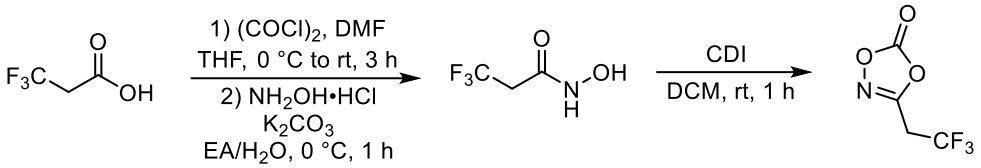
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (dd, J = 17.0, 1.6 Hz, 1H), 6.10 (dd, J = 17.0, 10.2 Hz, 1H), 6.06 (s, 1H), 5.61 (dd, J = 10.2, 1.6 Hz, 1H), 4.16 – 3.97 (m, 2H), 3.30 – 3.12 (m, 2H), 2.65 (t, J = 12.7 Hz, 2H), 1.73 – 1.61 (m, 3H), 1.42 (s, 9H), 1.19 – 1.04 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.82, 154.95, 130.86, 126.74, 79.57, 45.10, 43.76, 36.57, 29.92, 28.59.

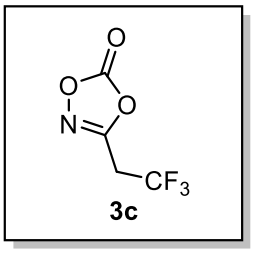
IR ($CDCl_3$, cm^{-1}) *v* 3302, 3080, 2976, 2926, 2854, 2244, 1658, 1546, 1424, 1365, 1226, 1167, 1143, 906, 727, 647.

HRMS (ESI) m/z $[C_{14}H_{24}N_2NaO_3]^+$ ($[M+Na]^+$) calculated 291.1685, found 291.1699.

Preparation of 3c



Oxalyl chloride (9.8 mmol, 0.98 equiv) and catalytic amount (5 – 10 drops) of DMF were added dropwise to a solution of 3,3,3-trifluoropropanoic acid (10 mmol, 1.0 equiv) in THF (0.3 M) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 hours. After the full conversion of acid, the crude material was taken without concentration. In a separate flask, hydroxylamine hydrochloride (11 mmol, 1.1 equiv) was dissolved in 0.1 M of ethyl acetate/H_2O 2:1 biphasic mixture. K_2CO_3 (20 mmol, 2 equiv) was added to the solution and cooled to 0 °C. The crude THF solution of acid chloride was added dropwise to the mixture and stirred for 1 hour at 0 °C. After completion of the reaction, the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was used without further purification. To a solution of 3,3,3-trifluoro-*N*-hydroxypropanamide (3.22 mmol, 1.0 equiv) in DCM (0.2 M), CDI (3.53 mmol, 1.2 equiv) was added as one portion. After stirring for 1 hour at room temperature, the reaction was quenched with 1 M HCl and extracted with DCM three times. The combined organic layer was washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure to afford 3-(2,2,2-trifluoroethyl)-1,4,2-dioxazol-5-one (**3c**). No further purification was required.



3c

Yield: 44% (over 2 steps), 2.05 mmol, 346 mg, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (q, J = 9.1 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.61 (q, J = 3.9 Hz), 153.03, 122.37 (q, J = 278.2 Hz), 31.48 (q, J = 34.9 Hz).

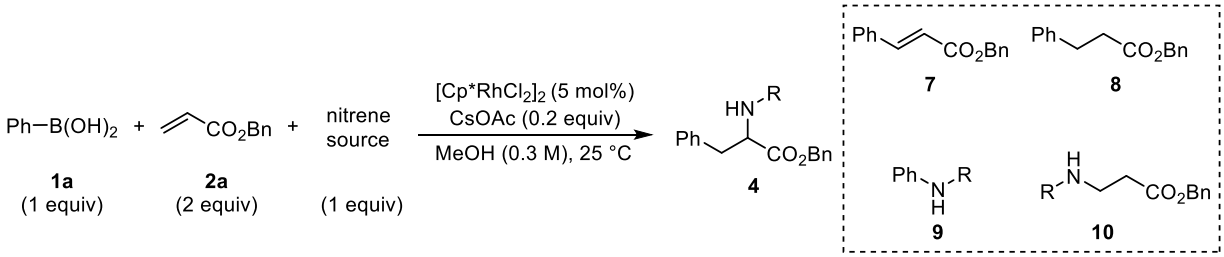
^{19}F NMR (376 MHz, $CDCl_3$) δ -63.40 (t, J = 9.1 Hz).

3. General procedure for the carboamination of alkenes

$[Cp^*RhCl_2]_2$ (0.0050 mmol, 5 mol%), sodium bicarbonate (0.03 mmol, 0.3 equiv), and boronic acid (0.25 mmol, 2.5 equiv) were measured in a 0.5-dram vial with a magnetic stir bar. In a separate vial, dioxazolone (0.1 mmol, 1 equiv) and alkene (0.3 mmol, 3 equiv) were dissolved in 0.10 mL of MeOH and transferred to the first vial. It was rinsed with an additional 0.07 mL of MeOH and transferred again to the first vial. The reaction mixture was then stirred at 25 ^{o}C for 16 hours. After the completion of the reaction, the solvent was removed by a rotary evaporator. Ethyl acetate was added to the residue and filtered through a short pad of celite and washed with ethyl acetate three times. The filtrate was concentrated by rotary evaporator and a crude ^{1}H NMR spectrum was collected with 1,3,5-trimethoxybenzene as the internal standard. Purification was performed by flash chromatography or preparational TLC using ethyl acetate and hexane or DCM and MeOH as the eluent.

4. Detailed optimization table

Table S1.[a]



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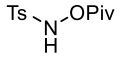
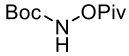
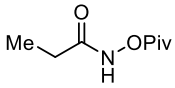
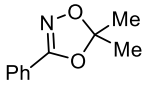
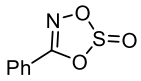
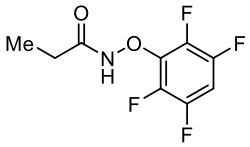
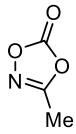
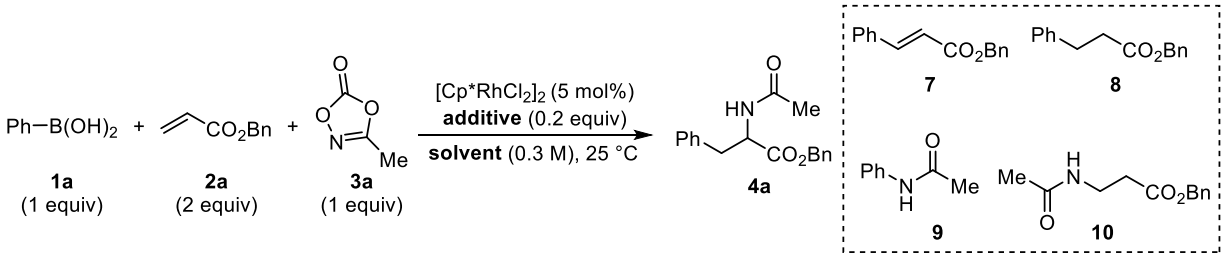
1		-	-	-	-	-
2		-	-	-	-	-
3		-	-	-	>95	-
4		-	-	-	>95	-
5		-	-	-	-	-
6		-	-	-	-	-
7		-	80	6	-	-
8		8	24	< 5	10	< 5

[a]Reaction were conducted on 0.1 mmol scale according to the general procedure. Yield was determined by ^{1}H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. The yield of side products was calculated based on 0.1 mmol.

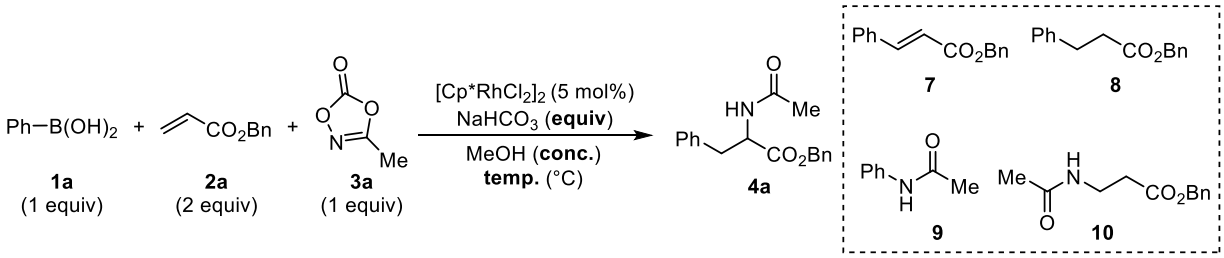
Table S2.[a]



entry	solvent (0.3 M)	additive (0.2 equiv)	**4a** (%)	**7** (%)	**8** (%)	**9** (%)	**10** (%)
1	MeOH	CsOAc	8	24	<5	10	<5
2	MeOH	CsOPiv	<5	13	<5	<5	<5
3	MeOH	Cs_2CO_3	48	28	<5	9	6
4	THF	Cs_2CO_3	29	20	<5	<5	6
5	TFE	Cs_2CO_3	16	20	<5	46	9
6	DCE	Cs_2CO_3	17	46	<5	21	11
7	EtOH	Cs_2CO_3	28	30	<5	24	<5
8	HFIP	Cs_2CO_3	<5	10	<5	35	6
9	MeCN	Cs_2CO_3	< 5	24	< 5	10	8
10	Acetone	Cs_2CO_3	15	22	< 5	7	< 5
11	*i*-PrOH	Cs_2CO_3	16	14	< 5	11	< 5
12	*t*-BuOH	Cs_2CO_3	6	10	< 5	8	< 5
13	MeOH	Li_2CO_3	44	30	6	9	<5
14	MeOH	Na_2CO_3	45	29	6	8	5
15	MeOH	K_2CO_3	42	30	7	8	5
16	MeOH	$NaHCO_3$	44	28	8	8	<5
17	MeOH	NaF	48	33	<5	7	8
18	MeOH	NaOAc	<5	20	<5	6	<5

[a]Reaction were conducted on 0.1 mmol scale according to the general procedure. Yield was determined by ^{1}H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. The yield of side products was calculated based on 0.1 mmol.

Table S3.[a]

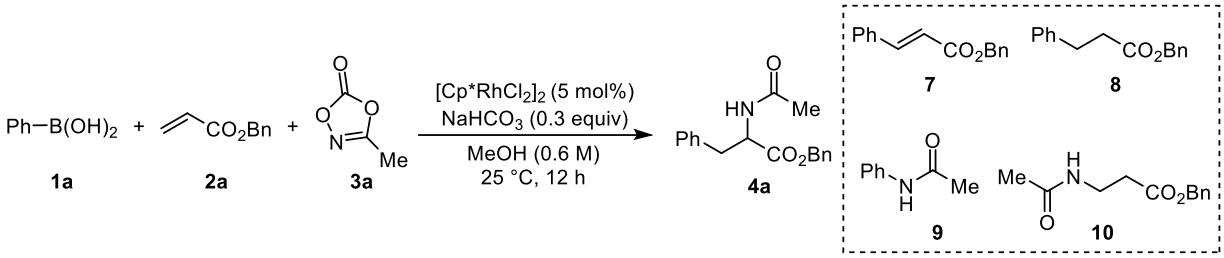


1a (1 equiv) + **2a** (2 equiv) + **3a** (1 equiv) → **4a**

entry	concentration (M)	additive (equiv)	temperature (°C)	**4a** (%)	**7** (%)	**8** (%)	**9** (%)	**10** (%)
1	0.1	$NaHCO_3$ (0.2)	25	32	32	7	8	9
2	0.3	$NaHCO_3$ (0.2)	25	45	24	5	8	6
3	0.6	$NaHCO_3$ (0.2)	25	59	22	<5	8	6
4	0.6	$NaHCO_3$ (0.1)	25	56	20	<5	8	6
5	0.6	$NaHCO_3$ (0.3)	25	59	20	<5	9	6
6	0.6	$NaHCO_3$ (0.6)	25	60	20	<5	8	6
7	0.6	$NaHCO_3$ (1.0)	25	59	20	<5	8	6
8	0.6	$NaHCO_3$ (0.3)	40	56	34	<5	11	13
9	0.6	$NaHCO_3$ (0.3)	60	42	40	< 5	13	20

[a]Reaction were conducted on 0.1 mmol scale according to the general procedure. Yield was determined by ^{1}H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. The yield of side products was calculated based on 0.1 mmol.

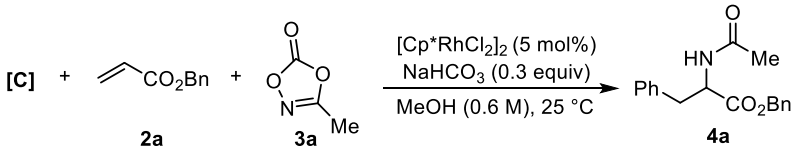
Table S4.[a]

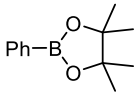


entry	**1a** (equiv) / **2a** (equiv) / **3a** (equiv)	**4a** (%)	**7** (%)	**8** (%)	**9** (%)	**10** (%)
1	1 / 1 / 1	55	20	<5	16	5
2	1 / 1 / 2	54	10	<5	35	<5
3	1 / 1 / 3	44	6	<5	51	<5
4	1 / 2 / 1	59	22	<5	8	6
5	1 / 3 / 1	57	22	<5	5	5
6	2 / 1 / 1	64	20	5	22	8
7	3 / 1 / 1	58	16	<5	24	7
8	2 / 2 / 1	71	36	<5	8	13
9	3 / 2 / 1	73	32	< 5	9	14
10	4 / 2 / 1	75	34	6	9	15
11	2 / 3 / 1	76	30	<5	6	15
12	2 / 4 / 1	76	32	<5	<5	15
13	3 / 3 / 1	77	34	<5	<5	15
14	2.5 / 3 / 1	77	35	< 5	<5	15

[a]Reaction were conducted on 0.1 mmol scale according to the general procedure. Yield was determined by ^{1}H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. The yield of side products was calculated based on 0.1 mmol.

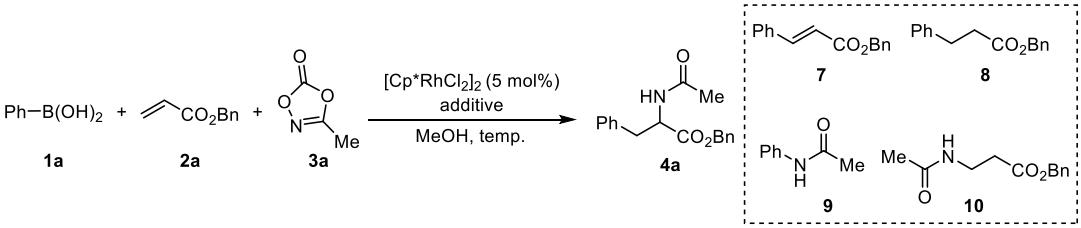
Table S5.[a]



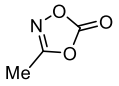
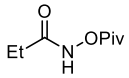
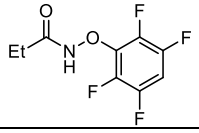
entry	**carbon source** (2.5 equiv)	yield (%)
1	Ph–B(OH)$_2$	77
2		39
3	Ph–BF$_3$K	trace

[a]Reaction were conducted on 0.1 mmol scale according to the general procedure. Yield was determined by ^{1}H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

Table S6. Summary of the detailed optimization table.



- Different nitrene sources give different side products.

nitrene source	**4a** (%)	**7** (%)	**8** (%)	**9** (%)	**10** (%)
	8	24	< 5	10	<5
	-	-	-	>95	-
	-	80	6	-	-

1a (1 equiv), **2a** (2 equiv), **3a** (1 equiv), CsOAc (0.2 equiv), MeOH (0.3 M)

- Acetates inhibit product formation, **7** becomes major product.

additive	**4a** (%)	**7** (%)	**8** (%)	**9** (%)	**10** (%)
$NaHCO_3$	44	28	8	8	5
NaOAc	<5	20	<5	6	<5

1a (1 equiv), **2a** (2 equiv), **3a** (1 equiv), additive (0.2 equiv), MeOH (0.3 M)

- Acidic solvent leads to more direct C-N coupling product (**9**).

solvent	**4a** (%)	**7** (%)	**8** (%)	**9** (%)	**10** (%)
MeOH	48	28	<5	9	6
TFE	16	20	<5	46	9

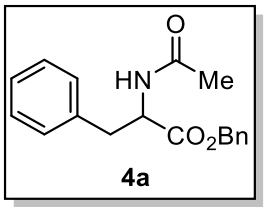
1a (1 equiv), **2a** (2 equiv), **3a** (1 equiv), Cs_2CO_3 (0.3 equiv), MeOH (0.3 M)

- Higher temperature give low chemoselectivity

temperature	**4a** (%)	**7** (%)	**8** (%)	**9** (%)	**10** (%)
25 °C	59	20	<5	9	6
60 °C	42	40	<5	13	20

1a (1 equiv), **2a** (2 equiv), **3a** (1 equiv), $NaHCO_3$ (0.3 equiv), MeOH (0.6 M)

5. Product characterization



4a

Yield: 68%, 20 mg, white solid.

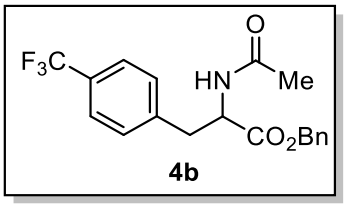
R_f = 0.26 (EA/Hex 2:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 3H), 7.31 – 7.26 (m, 2H), 7.26 – 7.17 (m, 3H), 7.04 – 6.95 (m, 2H), 5.93 (d, *J* = 7.9 Hz, 1H), 5.17 (d, *J* = 12.1 Hz, 1H), 5.12 (d, *J* = 12.1 Hz, 1H), 4.92 (dt, *J* = 7.9, 5.7 Hz, 1H), 3.18 – 3.03 (m, 2H), 1.98 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.62, 169.68, 135.82, 135.17, 129.43, 128.76, 128.72, 128.69, 128.67, 127.20, 67.40, 53.26, 37.94, 23.27.

IR ($CDCl_3$, cm^{-1}) *v* 3277, 3063, 3031, 2932, 1738, 1652, 1540, 1372, 1209, 1173, 734, 696.

HRMS (ASAP) m/z $[C_{18}H_{20}NO_3]^+$ ($[M+H]^+$) calculated 298.1443, found 298.1437.



4b

Yield: 62%, 23 mg, white solid.

R_f = 0.38 (EA/Hex 2:3).

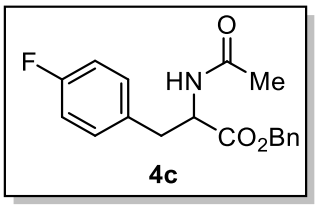
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.40 – 7.34 (m, 3H), 7.31 – 7.24 (m, 2H), 7.07 (d, *J* = 7.9 Hz, 2H), 5.98 (d, *J* = 7.3 Hz, 1H), 5.19 (d, *J* = 12.0 Hz, 1H), 5.09 (d, *J* = 12.0 Hz, 1H), 4.97 – 4.90 (m, 1H), 3.23 – 3.11 (m, 2H), 1.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.28, 169.74, 140.03 (d, *J* = 1.6 Hz), 134.89, 129.80, 129.45 (q, *J* = 32.7 Hz), 128.92, 128.84, 125.51 (q, *J* = 3.7 Hz), 124.17 (q, *J* = 270.9 Hz), 67.66, 53.10, 37.80, 23.28.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.51.

IR ($CDCl_3$, cm^{-1}) *v* 3276, 3066, 3036, 2939, 1740, 1654, 1541, 1324, 1164, 1122, 1067, 904, 729, 699.

HRMS (ASAP) m/z $[C_{19}H_{19}F_3NO_3]^+$ ($[M+H]^+$) calculated 366.1317, found 366.1310.



4c

Yield: 60%, 20 mg, white solid

$\mathbf{R}_f$ = 0.25 (EA/Hex 2:3).

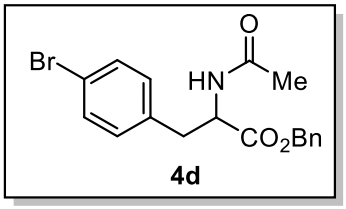
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 3H), 7.33 – 7.19 (m, 2H), 6.96 – 6.84 (m, 4H), 5.97 (d, *J* = 7.7 Hz, 1H), 5.19 (d, *J* = 12.0 Hz, 1H), 5.10 (d, *J* = 12.1 Hz, 1H), 4.89 (dt, *J* = 7.8, 5.7 Hz, 1H), 3.15 – 3.00 (m, 2H), 1.98 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.49, 169.69, 162.08 (d, *J* = 245.4 Hz), 135.05, 131.51 (d, *J* = 3.3 Hz), 130.91 (d, *J* = 8.0 Hz), 128.85, 128.81, 115.48 (d, *J* = 21.3 Hz), 67.50, 53.30, 37.17, 23.28. (Two aromatic peaks overlapped).

^{19}F NMR (376 MHz, $CDCl_3$) δ -115.54 – -115.76 (m).

IR ($CDCl_3$, cm^{-1}) *v* 3278, 3066, 2935, 1738, 1653, 1541, 1508, 1373, 1220, 1176, 905, 828, 729, 698.

HRMS (ASAP) m/z $[C_{18}H_{19}FNO_3]^+$ ($[M+H]^+$) calculated 316.1349, found 316.1348.



4d

Yield: 65%, 25 mg, white solid.

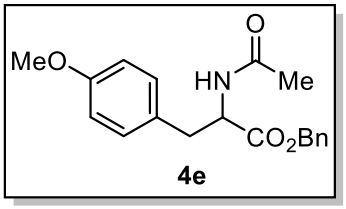
$\mathbf{R}_f$ = 0.31 (EA/Hex 2:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 3H), 7.33 – 7.25 (m, 4H), 6.87 – 6.79 (m, 2H), 5.96 (d, *J* = 7.7 Hz, 1H), 5.19 (d, *J* = 12.0 Hz, 1H), 5.09 (d, *J* = 12.1 Hz, 1H), 4.89 (dt, *J* = 7.8, 5.7 Hz, 1H), 3.13 – 2.99 (m, 2H), 1.98 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.38, 169.70, 134.99, 134.84, 131.73, 131.14, 128.87, 128.85, 128.83, 121.21, 67.54, 53.11, 37.40, 23.26.

IR ($CDCl_3$, cm^{-1}) v 3277, 3063, 3034, 2930, 1739, 1652, 1539, 1488, 1209, 1128, 1071, 813, 749.

HRMS (ASAP) m/z $[C_{18}H_{19}BrNO_3]^+$ ($[M+H]^+$) calculated 376.0548, found 376.0555.



4e

Yield: 60%, 20 mg, white solid.

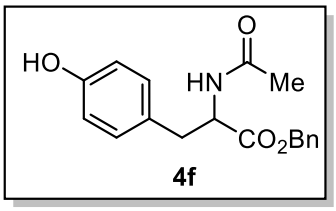
R_f = 0.33 (EA/Hex 2:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 3H), 7.33 – 7.27 (m, 2H), 6.94 – 6.86 (m, 2H), 6.78 – 6.70 (m, 2H), 5.91 (d, J = 7.9 Hz, 1H), 5.17 (d, J = 12.1 Hz, 1H), 5.11 (d, J = 12.1 Hz, 1H), 4.88 (dt, J = 7.9, 5.7 Hz, 1H), 3.76 (s, 3H), 3.14 – 3.00 (m, 2H), 1.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.70, 169.69, 158.76, 135.17, 130.40, 128.72, 128.66, 127.68, 114.05, 67.33, 55.29, 53.38, 37.05, 23.26. (Two aromatic peaks overlapped)

IR ($CDCl_3$, cm^{-1}) v 3278, 3063, 3034, 2953, 2934, 2836, 1739, 1653, 1511, 1373, 1246, 1177, 1033, 698.

HRMS (ASAP) m/z $[C_{19}H_{22}NO_4]^+$ ($[M+H]^+$) calculated 328.1549, found 328.1549.



4f

Yield: 70%, 22 mg, white solid.

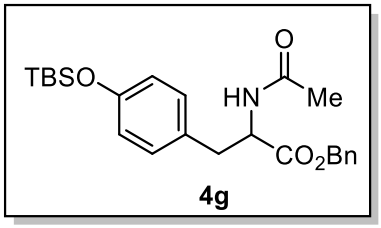
R_f = 0.17 (EA/Hex 2:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.23 (m, 5H), 7.02 (s, 1H), 6.87 – 6.79 (m, 2H), 6.77 – 6.62 (m, 2H), 6.10 (d, J = 8.1 Hz, 1H), 5.18 (d, J = 12.1 Hz, 1H), 5.12 (d, J = 12.1 Hz, 1H), 4.90 (dt, J = 8.0, 5.9 Hz, 1H), 3.06 (dd, J = 14.1, 5.8 Hz, 1H), 2.97 (dd, J = 14.1, 6.0 Hz, 1H), 1.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.84, 170.51, 155.65, 135.10, 130.43, 128.78, 128.73, 128.71, 126.90, 115.70, 67.52, 53.54, 37.22, 23.16.

IR ($CDCl_3$, cm^{-1}) ν 3298, 3062, 3033, 2930, 1737, 1652, 1514, 1451, 1374, 1213, 905, 730, 699.

HRMS (ASAP) m/z $[C_{18}H_{20}NO_4]^+$ ($[M+H]^+$) calculated 314.1392, found 314.1390.



4g

Yield: 66%, 28 mg, colorless oil.

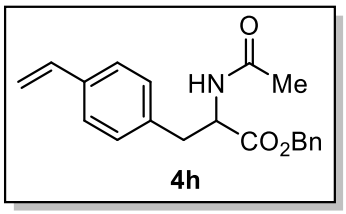
R_f = 0.38 (EA/Hex 2:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 5H), 6.89 – 6.79 (m, 2H), 6.73 – 6.63 (m, 2H), 5.89 (d, J = 7.9 Hz, 1H), 5.16 (d, J = 12.1 Hz, 1H), 5.11 (d, J = 12.2 Hz, 1H), 4.88 (dt, J = 7.9, 5.7 Hz, 1H), 3.11 – 2.96 (m, 2H), 1.97 (s, 3H), 0.97 (s, 9H), 0.18 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.71, 169.65, 154.88, 135.24, 130.41, 128.77, 128.72, 128.67, 128.36, 120.21, 67.36, 53.35, 37.16, 25.79, 23.28, 18.30, -4.29.

IR ($CDCl_3$, cm^{-1}) ν 3282, 3063, 3033, 2954, 2930, 2888, 2857, 1740, 1655, 1508, 1254, 906, 838, 728, 697.

HRMS (ASAP) m/z $[C_{24}H_{34}NO_4Si]^+$ ($[M+H]^+$) calculated 428.2257, found 428.2254.



4h

Yield: 55%, 18 mg, white solid.

R_f = 0.31 (EA/Hex 2:3).

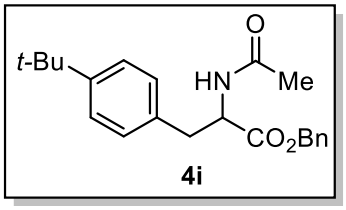
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 3H), 7.34 – 7.22 (m, 4H), 6.99 – 6.91 (m, 2H), 6.67 (dd, J = 17.6, 10.9 Hz, 1H), 5.94 (d, J = 7.9 Hz, 1H), 5.70 (dd, J = 17.6, 1.0 Hz, 1H), 5.23 (dd, J = 10.9, 0.9 Hz,

1H), 5.17 (d, *J* = 12.1 Hz, 1H), 5.11 (d, *J* = 12.1 Hz, 1H), 4.92 (dt, *J* = 7.8, 5.8 Hz, 1H), 3.17 – 3.03 (m, 2H), 1.98 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.59, 169.72, 136.58, 136.51, 135.40, 135.12, 129.61, 128.77, 128.74, 128.70, 126.50, 113.90, 67.43, 53.25, 37.69, 23.27.

IR ($CDCl_3$, cm^{-1}) *v* 3278, 3063, 2930, 2252, 1739, 1654, 1539, 1511, 1373, 1209, 1178, 904, 727, 699, 649.

HRMS (ASAP) m/z $[C_{20}H_{22}NO_3]^+$ ($[M+H]^+$) calculated 324.1600, found 324.1605.



4i

Yield: 55%, 19 mg, white solid.

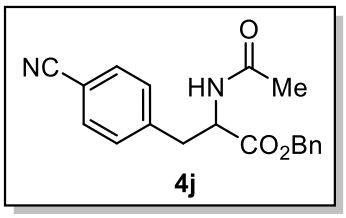
R_f = 0.37 (EA/Hex 2:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 3H), 7.32 – 7.27 (m, 2H), 7.26 – 7.22 (m, 2H), 6.97 – 6.91 (m, 2H), 5.93 (d, *J* = 7.7 Hz, 1H), 5.18 – 5.09 (m, 2H), 4.92 (dt, *J* = 7.9, 5.7 Hz, 1H), 3.08 (d, *J* = 5.7 Hz, 2H), 1.98 (s, 3H), 1.29 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.76, 169.74, 150.05, 135.21, 132.63, 129.10, 128.74, 128.70, 128.66, 125.60, 67.39, 53.26, 37.39, 34.55, 31.45, 23.29.

IR ($CDCl_3$, cm^{-1}) *v* 3280, 3062, 3033, 2960, 2868, 1740, 1654, 1537, 1515, 1368, 1190, 906, 730, 697.

HRMS (ASAP) m/z $[C_{22}H_{28}NO_3]^+$ ($[M+H]^+$) calculated 354.2069, found 354.2072.



4j

Yield: 51%, 16 mg, yellow oil.

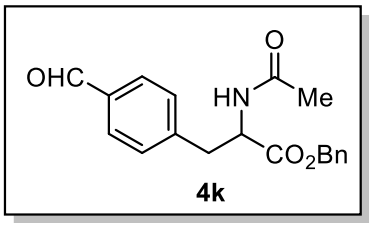
R_f = 0.23 (EA/Hex 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.38 (m, 2H), 7.42 – 7.31 (m, 3H), 7.31 – 7.28 (m, 2H), 7.08 – 7.02 (m, 2H), 6.03 (d, *J* = 7.5 Hz, 1H), 5.22 (d, *J* = 12.0 Hz, 1H), 5.08 (d, *J* = 11.9 Hz, 1H), 4.92 (dt, *J* = 7.5, 5.8 Hz, 1H), 3.16 (qd, *J* = 13.8, 5.9 Hz, 2H), 1.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.07, 169.75, 141.57, 134.82, 132.27, 130.22, 129.01, 128.99, 128.86, 118.76, 111.11, 67.70, 53.00, 38.13, 23.24.

IR ($CDCl_3$, cm^{-1}) *v* 3283, 3064, 3035, 2936, 2228, 1736, 1656, 1534, 1505, 1374, 1268, 1211, 1175, 905, 731, 698.

HRMS (ASAP) m/z $[C_{19}H_{19}N_2O_3]^+$ ($[M+H]^+$) calculated 323.1396, found 323.1390.



4k

Yield: 64%, 21 mg, white solid.

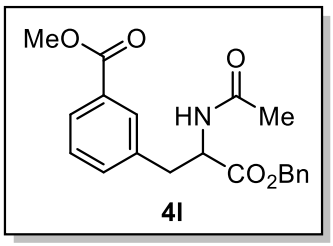
R_f = 0.20 (EA/Hex 2:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.73 – 7.66 (m, 2H), 7.41 – 7.31 (m, 3H), 7.32 – 7.27 (m, 2H), 7.17 – 7.10 (m, 2H), 6.05 (d, *J* = 7.7 Hz, 1H), 5.20 (d, *J* = 12.1 Hz, 1H), 5.10 (d, *J* = 12.0 Hz, 1H), 4.96 (dt, *J* = 7.7, 5.9 Hz, 1H), 3.19 (qd, *J* = 13.8, 5.9 Hz, 2H), 1.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.90, 171.23, 169.76, 143.15, 135.40, 134.90, 130.15, 129.97, 128.90, 128.89, 128.83, 67.63, 53.06, 38.20, 23.24.

IR ($CDCl_3$, cm^{-1}) *v* 3284, 3062, 3034, 2932, 2831, 2738, 2251, 1738, 1695, 1656, 1606, 1534, 1374, 1306, 1211, 1170, 905, 730, 698.

HRMS (ASAP) m/z $[C_{19}H_{20}NO_4]^+$ ($[M+H]^+$) calculated 326.1392, found 326.1387.



4l

Yield: 65%, 23 mg, yellow oil.

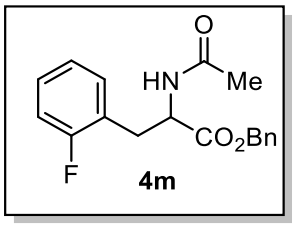
R_f = 0.19 (EA/Hex 2:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.79 (t, *J* = 1.8 Hz, 1H), 7.41 – 7.32 (m, 3H), 7.36 – 7.24 (m, 3H), 7.19 (dt, *J* = 7.7, 1.5 Hz, 1H), 6.04 (d, *J* = 7.8 Hz, 1H), 5.28 – 5.09 (m, 2H), 4.94 (dt, *J* = 7.7, 5.9 Hz, 1H), 3.89 (s, 3H), 3.20 (dd, *J* = 13.8, 6.0 Hz, 1H), 3.13 (dd, *J* = 13.9, 5.7 Hz, 1H), 1.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.42, 169.79, 166.94, 136.35, 134.99, 133.92, 130.58, 130.49, 128.77, 128.73, 128.68, 128.46, 67.57, 53.28, 52.25, 37.79, 23.22. (Two aromatic peaks overlapped)

IR ($CDCl_3$, cm^{-1}) *v* 3282, 3064, 3034, 2951, 1719, 1655, 1537, 1436, 1283, 1202, 1109, 908, 747, 733, 697.

HRMS (ASAP) m/z $[C_{20}H_{22}NO_5]^+$ ($[M+H]^+$) calculated 356.1498, found 356.1502.



4m

Yield: 74%, 23 mg, yellow oil.

R_f = 0.45 (EA/Hex 2:3).

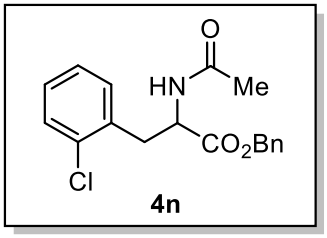
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 – 7.33 (m, 3H), 7.33 – 7.28 (m, 2H), 7.24 – 7.17 (m, 1H), 7.08 – 6.95 (m, 3H), 6.04 (d, *J* = 8.0 Hz, 1H), 5.17 (d, *J* = 12.2, 1H), 5.12 (d, *J* = 12,2 Hz, 1H), 4.91 (dt, *J* = 8.0, 6.0 Hz, 1H), 3.22 (ddd, *J* = 13.9, 6.0, 1.2 Hz, 1H), 3.12 (ddd, *J* = 13.9, 6.1, 1.1 Hz, 1H), 1.96 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.52, 169.79, 161.48 (d, *J* = 245.2 Hz), 135.17, 131.80 (d, *J* = 5.1 Hz), 129.12 (d, *J* = 8.3 Hz), 128.73, 128.64, 128.60, 124.32 (d, *J* = 3.9 Hz), 123.02 (d, *J* = 16.0 Hz), 115.49 (d, *J* = 22.5 Hz), 67.56, 52.67, 31.52 (d, *J* = 1.8 Hz), 23.17.

^{19}F NMR (376 MHz, $CDCl_3$) δ -117.50 (m).

IR ($CDCl_3$, cm^{-1}) *v* 3277, 3064, 3036, 2936, 1739, 1654, 1539, 1493, 1454, 1373, 1271, 1209, 1230, 1176, 1132, 755, 697.

HRMS (ASAP) m/z $[C_{18}H_{19}FNO_3]^+$ ($[M+H]^+$) calculated 316.1349, found 316.1350.



Yield: 37%, 12 mg, colorless liquid.

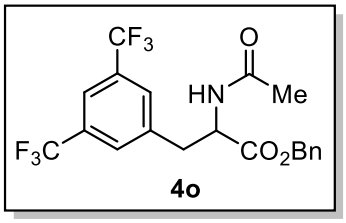
R_f = 0.26 (EA/Hex 2:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 6H), 7.21 – 7.05 (m, 3H), 6.01 (d, J = 8.2 Hz, 1H), 5.17 (d, J = 12.2 Hz, 1H), 5.12 (d, J = 12.2 Hz, 1H), 4.96 (ddd, J = 8.2, 7.1, 6.3 Hz, 1H), 3.32 (dd, J = 13.9, 6.3 Hz, 1H), 3.18 (dd, J = 13.9, 7.1 Hz, 1H), 1.95 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.65, 169.76, 135.18, 134.62, 134.17, 131.46, 129.78, 128.73, 128.69, 128.61, 128.50, 127.08, 67.52, 52.70, 35.55, 23.23.

IR ($CDCl_3$, cm^{-1}) v 3275, 3064, 2939, 1742, 1653, 1543, 1444, 1373, 1269, 1177, 1134, 1052, 751, 697.

HRMS (ASAP) m/z $[C_{18}H_{19}ClNO_3]^+$ ($[M+H]^+$) calculated 332.1053, found 332.1052.



Yield: 52%, 23 mg, white solid.

R_f = 0.46 (EA/Hex 2:3).

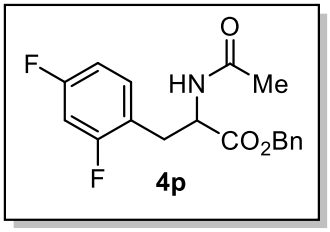
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.54 – 7.49 (m, 2H), 7.42 – 7.33 (m, 3H), 7.33 – 7.25 (m, 2H), 6.07 (d, J = 7.2 Hz, 1H), 5.14 (s, 2H), 4.93 (ddd, J = 7.2, 6.4, 5.3 Hz, 1H), 3.32 (dd, J = 13.9, 6.3 Hz, 1H), 3.21 (dd, J = 13.9, 5.3 Hz, 1H), 2.00 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.93, 169.87, 138.76, 134.58, 131.84 (q, J = 33.3 Hz), 129.72 (d, J = 3.9 Hz), 129.03, 128.94, 128.63, 123.31 (q, J = 272.7 Hz), 121.24 (p, J = 3.9 Hz), 67.95, 53.19, 37.62, 23.13.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.87 (s).

IR ($CDCl_3$, cm^{-1}) v 3271, 3068, 2957, 1741, 1654, 1545, 1378, 1276, 1171, 1129, 900, 700, 682.

HRMS (ASAP) m/z $[C_{20}H_{18}F_6NO_3]^+$ ($[M+H]^+$) calculated 434.1191, found 434.1189.



4p

Yield: 65%, 22 mg, colorless oil.

$\mathbf{R}_f$ = 0.28 (EA/Hex 2:3).

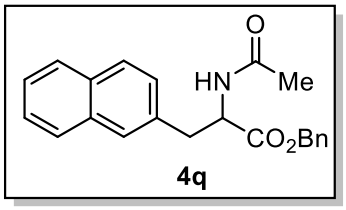
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 6.97 (td, *J* = 8.6, 6.3 Hz, 1H), 6.78 – 6.67 (m, 2H), 6.03 (d, *J* = 7.9 Hz, 1H), 5.14 (s, 2H), 4.89 (dt, *J* = 7.9, 6.0 Hz, 1H), 3.19 (ddd, *J* = 14.1, 6.1, 1.2 Hz, 1H), 3.07 (dd, *J* = 14.1, 5.9 Hz, 1H), 1.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.41, 169.77, 162.26 (dd, *J* = 248.4, 12.1 Hz), 161.42 (dd, *J* = 247.8, 11.9 Hz), 135.05, 132.37 (dd, *J* = 9.6, 6.2 Hz), 128.77, 128.75, 128.70, 118.91 (dd, *J* = 16.3, 3.8 Hz), 111.46 (dd, *J* = 21.2, 3.7 Hz), 103.93 (dd, *J* = 25.7, 26.0 Hz), 67.66, 52.61, 31.10, 23.18.

^{19}F NMR (376 MHz, $CDCl_3$) δ -111.23 (p, *J* = 7.7 Hz), -113.16 (q, *J* = 8.7 Hz).

IR ($CDCl_3$, cm^{-1}) *v* 3278, 3066, 3029, 2939, 1740, 1654, 1540, 1504, 1374, 1273, 1174, 1136, 1094, 965, 850, 747, 697.

HRMS (ASAP) m/z $[C_{18}H_{18}F_2NO_3]^+$ ($[M+H]^+$) calculated 334.1255, found 334.1255.



4q

Yield: 52%, 18 mg, white solid.

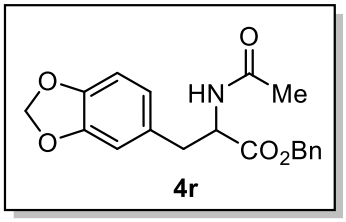
$\mathbf{R}_f$ = 0.26 (EA/Hex 2:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.6 Hz, 1H), 7.89 – 7.80 (m, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.55 – 7.41 (m, 2H), 7.34 – 7.23 (m, 4H), 7.20 – 7.09 (m, 3H), 5.99 (d, *J* = 7.8 Hz, 1H), 5.10 – 4.97 (m, 3H), 3.65 – 3.49 (m, 2H), 1.91 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.88, 169.84, 135.03, 134.01, 132.46, 132.37, 128.93, 128.67, 128.58, 128.49, 128.06, 127.63, 126.42, 125.90, 125.41, 123.72, 67.36, 53.47, 35.22, 23.23.

IR ($CDCl_3$, cm^{-1}) ν 3277, 3062, 2953, 2251, 1739, 1652, 1539, 1511, 1372, 1176, 905, 778, 728, 698.

HRMS (ASAP) m/z $[C_{22}H_{22}NO_3]^+$ ($[M+H]^+$) calculated 348.1600, found 348.1603.



4r

Yield: 65%, 22 mg, white solid.

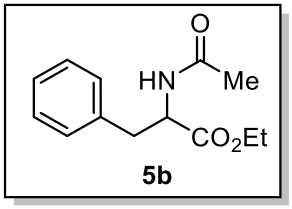
R_f = 0.37 (EA/Hex 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 3H), 7.34 – 7.29 (m, 2H), 6.64 (d, J = 7.9 Hz, 1H), 6.49 (d, J = 1.7 Hz, 1H), 6.42 (dd, J = 7.9, 1.7 Hz, 1H), 5.95 (d, J = 8.0 Hz, 1H), 5.91 (s, 2H), 5.18 (d, J = 12.1 Hz, 1H), 5.12 (d, J = 12.1 Hz, 1H), 4.87 (dt, J = 7.8, 5.7 Hz, 1H), 3.07 – 2.98 (m, 2H), 1.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.59, 169.70, 147.87, 146.81, 135.14, 129.40, 128.79, 128.74, 128.71, 122.53, 109.71, 108.41, 101.09, 67.43, 53.42, 37.68, 23.31.

IR ($CDCl_3$, cm^{-1}) ν 3281, 3065, 3034, 2927, 2893, 1738, 1654, 1537, 1501, 1489, 1443, 1371, 1246, 1191, 1037, 904, 729, 699.

HRMS (ASAP) m/z $[C_{19}H_{20}NO_5]^+$ ($[M+H]^+$) calculated 342.1341, found 342.1337.



5b

Yield: 68%, 16 mg, white solid.

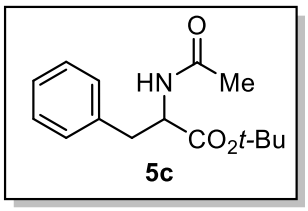
R_f = 0.30 (EA/Hex 2:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.19 (m, 3H), 7.14 – 7.07 (m, 2H), 5.93 (d, J = 7.8 Hz, 1H), 4.86 (dt, J = 7.9, 5.8 Hz, 1H), 4.17 (qd, J = 7.2, 1.2 Hz, 2H), 3.19 – 3.05 (m, 2H), 1.98 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.79, 169.72, 136.02, 129.42, 128.62, 127.18, 61.62, 53.26, 38.02, 23.25, 14.21.

IR ($CDCl_3$, cm^{-1}) ν 3283, 3063, 3030, 2982, 2932, 1737, 1656, 1542, 1374, 1212, 1028, 701.

HRMS (ASAP) m/z $[C_{13}H_{18}NO_3]^+$ ($[M+H]^+$) calculated 236.1287, found 236.1284.



5c

Yield: 63%, 17 mg, yellowish oil.

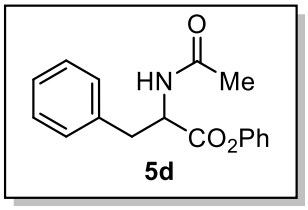
R_f = 0.31 (EA/Hex 2:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.18 (m, 3H), 7.18 – 7.05 (m, 2H), 5.97 (d, J = 7.7 Hz, 1H), 4.76 (dt, J = 7.8, 6.0 Hz, 1H), 3.09 (d, J = 6.0 Hz, 2H), 1.98 (s, 3H), 1.41 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.94, 169.64, 136.32, 129.62, 128.49, 127.08, 82.53, 53.65, 38.18, 28.07, 23.34.

IR ($CDCl_3$, cm^{-1}) ν 3285, 3064, 3030, 2978, 2931, 1732, 1655, 1544, 1498, 1369, 1257, 1226, 1154, 755, 738, 699.

HRMS (ESI) m/z $[C_{15}H_{21}NO_3Na]^+$ ($[M+H]^+$) calculated 286.1419, found 286.1433.



5d

Yield: 65%, 18 mg, white solid.

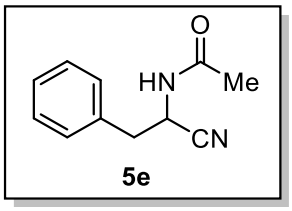
R_f = 0.28 (EA/Hex 2:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.19 (m, 8H), 7.03 – 6.95 (m, 2H), 6.04 (d, J = 7.8 Hz, 1H), 5.12 (dt, J = 7.7, 6.0 Hz, 1H), 3.34 – 3.20 (m, 2H), 2.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.50, 169.89, 150.38, 135.72, 129.63, 129.57, 128.86, 127.49, 126.33, 121.37, 53.44, 38.08, 23.23.

IR ($CDCl_3$, cm^{-1}) ν 3267, 3033, 2936, 1760, 1653, 1537, 1491, 1372, 1190, 1162, 1121, 908, 734, 699, 494.

HRMS (ESI) m/z $[C_{17}H_{18}NO_3]^+$ ($[M+H]^+$) calculated 284.1287, found 284.1281.



5e

Yield: 70%, 13 mg, white solid.

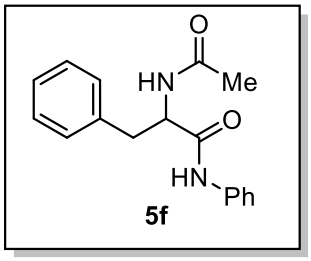
R_f = 0.27 (EA/Hex 2:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 3H), 7.31 – 7.24 (m, 2H), 6.17 (d, J = 8.6 Hz, 1H), 5.14 (ddd, J = 8.7, 7.4, 5.8 Hz, 1H), 3.08 (m, 2H), 1.98 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.56, 134.03, 129.57, 129.14, 128.09, 118.30, 41.66, 38.88, 22.89.

IR ($CDCl_3$, cm^{-1}) ν 3270, 3032, 2932, 2856, 2244, 1954, 1658, 1531, 1497, 1372, 1289, 749, 700.

HRMS (ASAP) m/z $[C_{11}H_{13}N_2O]^+$ ($[M+H]^+$) calculated 189.1028, found 189.1029.



5f

Yield: 71%, 20 mg, white solid.

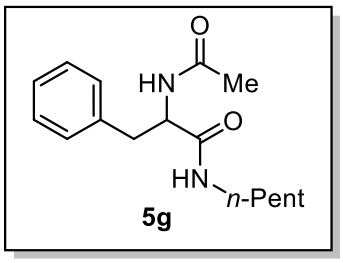
R_f = 0.42 (EA/Hex 2:3).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 8.27 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 7.9 Hz, 2H), 7.34 – 7.24 (m, 6H), 7.21 – 7.16 (m, 1H), 7.05 (t, J = 7.3 Hz, 1H), 4.66 (td, J = 8.9, 5.3 Hz, 1H), 3.02 (dd, J = 13.7, 5.3 Hz, 1H), 2.84 (dd, J = 13.7, 9.4 Hz, 1H), 1.79 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 170.34, 169.26, 138.81, 137.72, 129.14, 128.68, 128.06, 126.33, 123.37, 119.34, 54.86, 37.76, 22.39.

IR (DMSO-d_6, cm^{-1}) v 3446, 2249, 2123, 1767, 1665, 1548, 1222, 1052, 1024, 1006, 820, 757, 621.

HRMS (ASAP) m/z $[C_{17}H_{19}N_2O_2]^+$ ($[M+H]^+$) calculated 283.1447, found 283.1446.



5g

Yield: 59%, 16 mg, yellow solid.

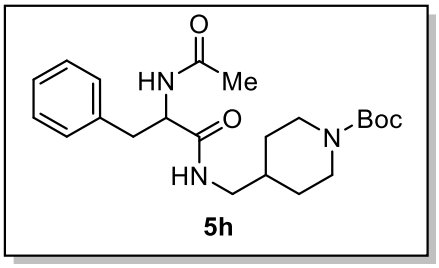
R_f = 0.29 (EA/Hex 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 2H), 7.27 – 7.16 (m, 3H), 6.70 (d, J = 8.1 Hz, 1H), 6.15 (t, J = 5.7 Hz, 1H), 4.64 (td, J = 8.3, 6.4 Hz, 1H), 3.24 – 3.11 (m, 1H), 3.10 – 2.94 (m, 3H), 1.96 (s, 3H), 1.40 – 1.18 (m, 4H), 1.23 – 1.06 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.96, 170.11, 137.01, 129.39, 128.67, 127.00, 54.93, 39.59, 39.03, 29.01, 28.99, 23.25, 22.38, 14.02.

IR ($CDCl_3$, cm^{-1}) v 3277, 3085, 3030, 2956, 2929, 2859, 1638, 1552, 1497, 1372, 743, 698.

HRMS (ASAP) m/z $[C_{16}H_{25}N_2O_2]^+$ ($[M+H]^+$) calculated 277.1916, found 277.1913.



5h

Yield: 74%, 30 mg, yellow oil.

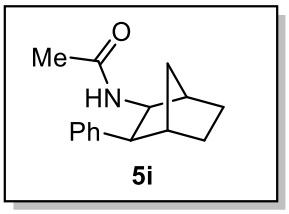
R_f = 0.22 (EA 100%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.12 (m, 5H), 6.63 (d, J = 8.1 Hz, 1H), 6.43 (t, J = 5.6 Hz, 1H), 4.68 (td, J = 8.5, 6.3 Hz, 1H), 4.00 (s, 2H), 3.22 – 3.08 (m, 1H), 3.03 (dd, J = 13.4, 6.3 Hz, 1H), 2.96 (dd, J = 13.4, 8.7 Hz, 1H), 2.86 (s, 1H), 2.66 – 2.45 (m, 2H), 1.96 (s, 3H), 1.43 (s, 9H), 1.41 – 1.21 (m, 3H), 1.01 – 0.84 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.19, 170.17, 154.86, 136.81, 129.37, 128.72, 127.06, 79.52, 54.95, 44.91, 43.75, 38.98, 36.21, 29.64, 28.56, 23.26.

IR ($CDCl_3$, cm^{-1}) v 3281, 2972, 2923, 2849, 1686, 1640, 1547, 1421, 1365, 1277, 1226, 1168, 1141, 734, 698.

HRMS (ESI) m/z $[C_{22}H_{33}N_3NaO_4]^+$ ($[M+Na]^+$) calculated 426.2369, found 426.2367.



5i

Yield: 61%, 14 mg, white solid.

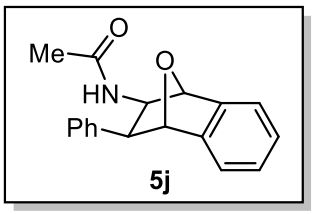
R_f = 0.42 (EA/Hex 2:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 2H), 7.32 – 7.22 (m, 3H), 4.79 (d, J = 8.7 Hz, 1H), 4.29 (t, J = 8.6 Hz, 1H), 3.19 (d, J = 8.6 Hz, 1H), 2.70 (s, 1H), 2.41 – 2.35 (m, 1H), 1.84 – 1.64 (m, 3H), 1.62 (s, 3H), 1.57 – 1.38 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.17, 140.13, 128.54, 128.40, 126.47, 56.52, 52.12, 42.61, 40.28, 35.54, 30.09, 26.39, 23.24.

IR ($CDCl_3$, cm^{-1}) v 3293, 3061, 2955, 2872, 1646, 1549, 1496, 1451, 1373, 1290, 1154, 905, 726, 700, 494.

HRMS (ASAP) m/z $[C_{15}H_{20}NO]^+$ ($[M+H]^+$) calculated 230.1545, found 230.1547.



Yield: 89%, 25 mg, white solid.

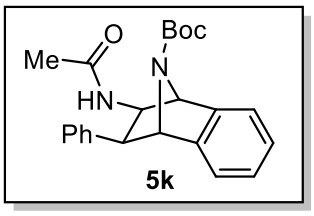
R_f = 0.42 (EA/Hex 2:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.26 (m, 7H), 7.30 – 7.20 (m, 2H), 5.56 (s, 1H), 5.31 – 5.23 (m, 2H), 4.49 (t, *J* = 8.5 Hz, 1H), 3.34 (d, *J* = 7.9 Hz, 1H), 1.58 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.86, 146.12, 143.36, 138.74, 128.93, 128.84, 127.64, 127.30, 127.27, 120.84, 119.13, 84.45, 84.30, 54.24, 50.12, 22.98.

IR ($CDCl_3$, cm^{-1}) *v* 3428, 3308, 3040, 3006, 1656, 1495, 1371, 904, 727, 703, 648.

HRMS (ASAP) m/z $[C_{18}H_{18}NO_2]^+$ ($[M+H]^+$) calculated 280.1338, found 280.1337.



Yield: 55%, 21 mg, white solid.

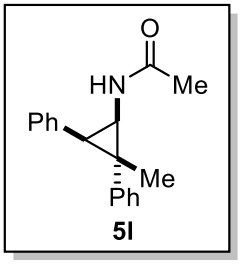
R_f = 0.26 (EA/Hex 2:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 1H), 7.35 – 7.28 (m, 2H), 7.28 – 7.20 (m, 4H), 7.19 – 7.13 (m, 2H), 5.26 (s, 1H), 5.18 (d, *J* = 9.4 Hz, 1H), 4.91 (s, 1H), 4.46 – 4.29 (m, 1H), 3.20 (d, *J* = 8.1 Hz, 1H), 1.51 (s, 3H), 1.34 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.62, 156.59, 146.57, 143.71, 138.95, 128.83, 128.68, 127.54, 127.29, 127.16, 121.79, 120.04, 99.74, 81.11, 67.68, 66.46, 53.64, 50.12, 28.44, 22.96. (Measured at 60 °C.)

IR ($CDCl_3$, cm^{-1}) *v* 3315, 3028, 2979, 2927, 1698, 1667, 1367, 1336, 1278, 1255, 1158, 909, 729.

HRMS (ESI) m/z $[C_{23}H_{26}N_2NaO_3]^+$ ($[M+Na]^+$) calculated 401.1841, found 401.1851.



5l

Yield: 43%, 11 mg, colorless oil.

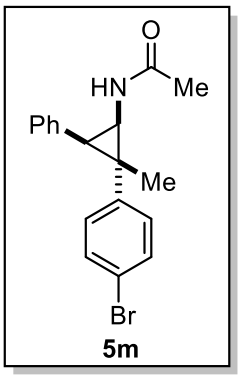
R_f = 0.37 (EA/Hex 2:3).

(major diastereomer) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 – 7.58 (m, 2H), 7.48 – 7.42 (m, 2H), 7.42 – 7.32 (m, 5H), 7.32 – 7.25 (m, 1H), 5.37 – 5.32 (m, 1H), 3.50 (dd, *J* = 8.6, 5.0 Hz, 1H), 2.69 (dd, *J* = 8.6, 1.2 Hz, 1H), 2.02 (s, 3H), 1.27 (s, 3H).

(major diastereomer) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.48, 146.83, 134.92, 130.58, 129.25, 128.74, 128.57, 127.14, 126.65, 37.19, 30.92, 30.24, 23.36, 18.07.

IR ($CDCl_3$, cm^{-1}) *v* 3303, 3056, 3024, 2927, 1651, 1601, 1495, 1444, 1370, 1268, 907, 763, 732, 700.

HRMS (ASAP) m/z $[C_{18}H_{20}NO]^+$ ($[M+H]^+$) calculated 266.1545, found 266.1544.



5m

Yield: 38%, 13 mg, white solid.

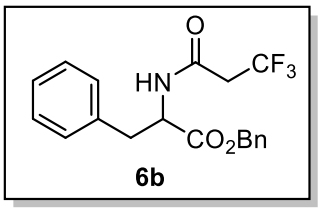
R_f = 0.32 (EA/Hex 2:3).

(major diastereomer) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.42 (m, 6H), 7.39 – 7.30 (m, 3H), 5.34 (s, 1H), 3.41 (dd, *J* = 8.7, 4.7 Hz, 1H), 2.65 (dd, *J* = 8.7, 1.1 Hz, 1H), 2.01 (s, 3H), 1.23 (s, 3H).

(major diastereomer) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.57, 145.93, 134.53, 131.83, 130.53, 130.46, 129.37, 127.32, 120.50, 37.15, 30.69, 30.17, 23.32, 17.94.

IR ($CDCl_3$, cm^{-1}) *v* 3302, 3054, 3026, 2931, 2979, 1653, 1492, 1444, 1369, 1090, 1009, 825, 734, 702, 532.

HRMS (ASAP) m/z $[C_{18}H_{19}BrNO]^+$ ($[M+H]^+$) calculated 344.0650, found 344.0644.



6b

Yield: 73%, 27 mg, white solid.

$\mathbf{R_f}$ = 0.30 (EA/Hex 1:4).

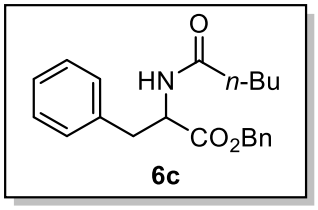
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 3H), 7.34 – 7.28 (m, 2H), 7.24 – 7.17 (m, 3H), 7.01 – 6.92 (m, 2H), 6.19 (d, *J* = 7.6 Hz, 1H), 5.20 (d, *J* = 12.1 Hz, 1H), 5.14 (d, *J* = 12.1 Hz, 1H), 4.94 (dt, *J* = 7.7, 5.6 Hz, 1H), 3.24 – 3.09 (m, 2H), 3.04 (q, *J* = 10.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.94, 162.13 (q, *J* = 3.6 Hz), 135.23, 134.94, 129.44, 128.85, 128.84, 128.77, 127.42, 123.97 (q, *J* = 276.9 Hz), 67.74, 53.59, 41.69 (q, *J* = 29.7 Hz), 37.68. (Two aromatic peaks overlapped)

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.86 (t, *J* = 10.5 Hz)

IR ($CDCl_3$, cm^{-1}) *v* 3313, 3066, 3032, 2957, 1740, 1664, 1542, 1388, 1261, 1240, 1213, 1191, 1136, 905, 733, 699.

HRMS (ASAP) m/z $[C_{19}H_{19}F_3NO_3]^+$ ($[M+H]^+$) calculated 366.1317, found 366.1319.



6c

Yield: 53%, 18 mg, white solid.

$\mathbf{R_f}$ = 0.23 (EA/Hex 1:4).

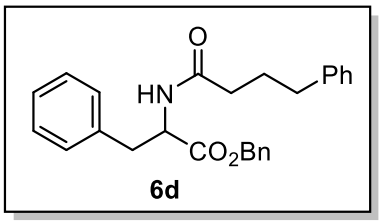
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 3H), 7.33 – 7.27 (m, 2H), 7.24 – 7.19 (m, 3H), 7.03 – 6.96 (m, 2H), 5.87 (d, *J* = 7.8 Hz, 1H), 5.17 (d, *J* = 12.2 Hz, 1H), 5.11 (d, *J* = 12.1 Hz, 1H), 4.95 (dt, *J* = 7.9, 5.8

Hz, 1H), 3.19 – 3.04 (m, 2H), 2.20 – 2.12 (m, 2H), 1.62 – 1.50 (m, 2H), 1.35 – 1.24 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.76, 171.72, 135.89, 135.20, 129.45, 128.75, 128.72, 128.68, 128.65, 127.17, 67.39, 53.04, 38.01, 36.40, 27.73, 22.42, 13.88.

IR ($CDCl_3$, cm^{-1}) *v* 3288, 3063, 3031, 2956, 2930, 2869, 1740, 1648, 1537, 1497, 1454, 1210, 1174, 742, 697.

HRMS (ASAP) m/z $[C_{21}H_{26}NO_3]^+$ ($[M+H]^+$) calculated 340.1913, found 340.1908.



6d

Yield: 54%, 22 mg, white solid.

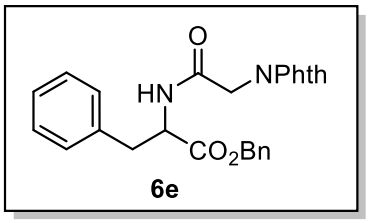
R_f = 0.25 (EA/Hex 1:4).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.08 (m, 13H), 7.04 – 6.95 (m, 2H), 5.86 (d, *J* = 7.9 Hz, 1H), 5.17 (d, *J* = 12.1 Hz, 1H), 5.11 (d, *J* = 12.1 Hz, 1H), 4.94 (dt, *J* = 7.9, 5.9 Hz, 1H), 3.19 – 3.03 (m, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 2.16 (dd, *J* = 7.9, 6.6 Hz, 2H), 1.92 (p, *J* = 7.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.37, 171.67, 141.50, 135.84, 135.17, 129.41, 128.74, 128.71, 128.67, 128.59, 128.49, 127.19, 126.06, 67.40, 53.07, 37.97, 35.70, 35.14, 27.01. (Two aromatic peaks overlapped)

IR ($CDCl_3$, cm^{-1}) *v* 3290, 3062, 3028, 2930, 2859, 1738, 1648, 1534, 1496, 1453, 1175, 907, 734, 696.

HRMS (ASAP) m/z $[C_{26}H_{28}NO_3]^+$ ($[M+H]^+$) calculated 402.2069, found 402.2067.



6e

Yield: 56%, 25 mg, white solid.

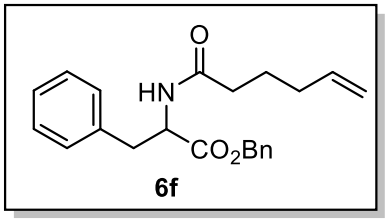
R_f = 0.44 (EA/Hex 2:3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.85 (m, 2H), 7.79 – 7.73 (m, 2H), 7.41 – 7.32 (m, 3H), 7.31 – 7.27 (m, 2H), 7.19 – 7.13 (m, 3H), 7.03 – 6.90 (m, 2H), 6.24 (d, *J* = 7.6 Hz, 1H), 5.18 (d, *J* = 12.1 Hz, 1H), 5.12 (d, *J* = 12.0 Hz, 1H), 4.91 (dt, *J* = 7.8, 5.5 Hz, 1H), 4.38 (d, *J* = 16.1 Hz, 1H), 4.30 (d, *J* = 16.1 Hz, 1H), 3.18 – 3.07 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.00, 167.76, 165.66, 135.39, 134.99, 134.38, 132.13, 129.58, 128.84, 128.80, 128.79, 128.68, 127.24, 123.80, 67.62, 53.53, 40.80, 37.69.

IR ($CDCl_3$, cm^{-1}) *v* 3346, 3066, 3033, 2947, 1774, 1716, 1419, 1393, 1192, 954, 904, 730, 716, 701.

HRMS (ASAP) m/z $[C_{26}H_{23}N_2O_5]^+$ ($[M+H]^+$) calculated 443.1607, found 4431608.



6f

Yield: 61%, 21 mg, colorless oil.

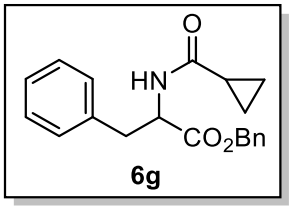
R_f = 0.22 (EA/Hex 1:4).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.33 (m, 3H), 7.33 – 7.28 (m, 2H), 7.24 – 7.19 (m, 3H), 7.03 – 6.96 (m, 2H), 5.86 (d, *J* = 7.9 Hz, 1H), 5.75 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.18 (d, *J* = 12.1 Hz, 1H), 5.12 (d, *J* = 12.1 Hz, 1H), 5.02 – 4.92 (m, 3H), 3.20 – 3.05 (m, 2H), 2.19 – 2.15 (m, 2H), 2.07 - 2.02 (m, 2H), 1.76 – 1.66 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.45, 171.68, 137.90, 135.86, 135.19, 129.44, 128.76, 128.73, 128.69, 128.67, 127.20, 115.48, 67.41, 53.06, 38.00, 35.76, 33.11, 24.64.

IR ($CDCl_3$, cm^{-1}) *v* 3293, 3064, 3031, 2931, 1742, 1648, 1539, 1498, 1454, 1175, 744, 698.

HRMS (ASAP) m/z $[C_{22}H_{26}NO_3]^+$ ($[M+H]^+$) calculated 352.1913, found 352.1911.



6g

Yield: 53%, 17 mg, white solid.

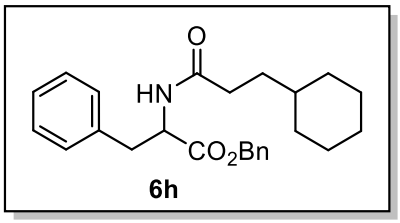
R_f = 0.27 (EA/Hex 1:4).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 3H), 7.32 – 7.28 (m, 2H), 7.25 – 7.19 (m, 3H), 7.07 – 6.98 (m, 2H), 6.10 (d, *J* = 7.8 Hz, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 5.12 (d, *J* = 12.1 Hz, 1H), 4.95 (dt, *J* = 7.9, 5.8 Hz, 1H), 3.18 – 3.07 (m, 2H), 1.36 (tt, *J* = 7.9, 4.6 Hz, 1H), 1.02 – 0.91 (m, 2H), 0.79 – 0.68 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.24, 171.74, 135.92, 135.21, 129.51, 128.74, 128.71, 128.66, 128.64, 127.15, 67.35, 53.34, 38.10, 14.75, 7.52, 7.45.

IR ($CDCl_3$, cm^{-1}) *v* 3302, 3063, 3029, 3006, 2941, 2838, 1739, 1650, 1599, 1498, 1455, 1203, 1150, 1066, 732, 699.

HRMS (ASAP) m/z $[C_{20}H_{22}NO_3]^+$ ($[M+H]^+$) calculated 324.1600, found 324.1601.



6h

Yield: 57%, 22 mg, colorless oil.

R_f = 0.33 (EA/Hex 1:4).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.31 (m, 3H), 7.34 – 7.28 (m, 2H), 7.28 – 7.18 (m, 3H), 7.04 – 6.95 (m, 2H), 5.86 (d, *J* = 7.8 Hz, 1H), 5.18 (d, *J* = 12.1 Hz, 1H), 5.12 (d, *J* = 12.1 Hz, 1H), 4.95 (dt, *J* = 7.9, 5.8 Hz, 1H), 3.19 – 3.05 (m, 2H), 2.24 – 2.12 (m, 2H), 1.74 – 1.59 (m, 5H), 1.54 – 1.42 (m, 2H), 1.28 – 1.05 (m, 4H), 0.94 – 0.79 (m, 2H).

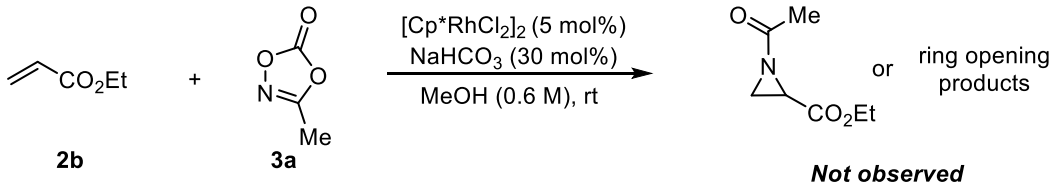
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.03, 171.73, 135.89, 135.21, 129.46, 128.76, 128.73, 128.68, 128.64, 127.18, 67.39, 53.05, 38.00, 37.34, 34.16, 33.17, 33.11, 33.03, 26.65, 26.33.

IR ($CDCl_3$, cm^{-1}) *v* 3298, 3070, 3029, 2921, 2850, 1740, 1648, 1536, 1498, 1451, 1174, 905, 730, 698.

HRMS (ASAP) m/z $[C_{25}H_{32}NO_3]^+$ ($[M+H]^+$) calculated 394.2387, found 394.2384.

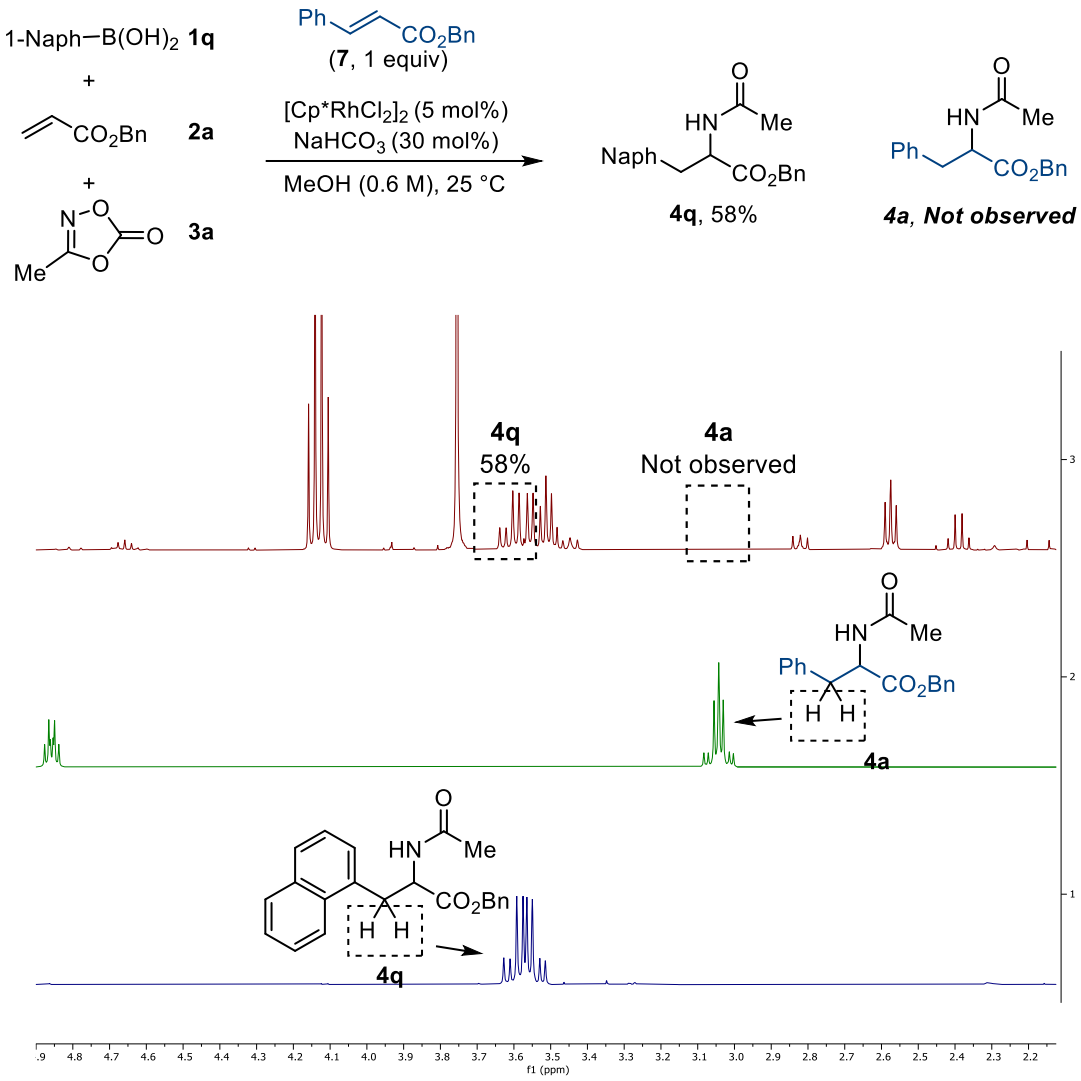
6. Mechanistic studies

Possible aziridine intermediate



$[Cp^*RhCl_2]_2$ (0.0050 mmol, 5 mol%) and sodium bicarbonate (0.03 mmol, 30 mol%) were measured in a 0.5-dram vial with a magnetic stir bar. In a separate vial, dioxazolone **3a** (0.1 mmol, 1 equiv) and ethyl acrylate **2b** (0.3 mmol, 3 equiv) were dissolved in 0.10 mL of MeOH and transferred to the first vial. It was rinsed with an additional 0.07 mL of MeOH and transferred again to the first vial. The reaction mixture was then stirred at room temperature for 16 hours. After the completion of the reaction, the solvent was removed by rotary evaporator. Ethyl acetate was added to the residue and filtered through a short pad of celite and washed with ethyl acetate three times. The filtrate was concentrated by rotary evaporator and a crude ^1H NMR spectrum was collected with 1,3,5-trimethoxybenzene as the internal standard. As a result, neither aziridine nor ring-opening products by methanol were observed. This result suggests Rh(III)-catalyzed aziridination and subsequent ring-opening by phenylboronic acid is unlikely for the mechanism of the carboamination.

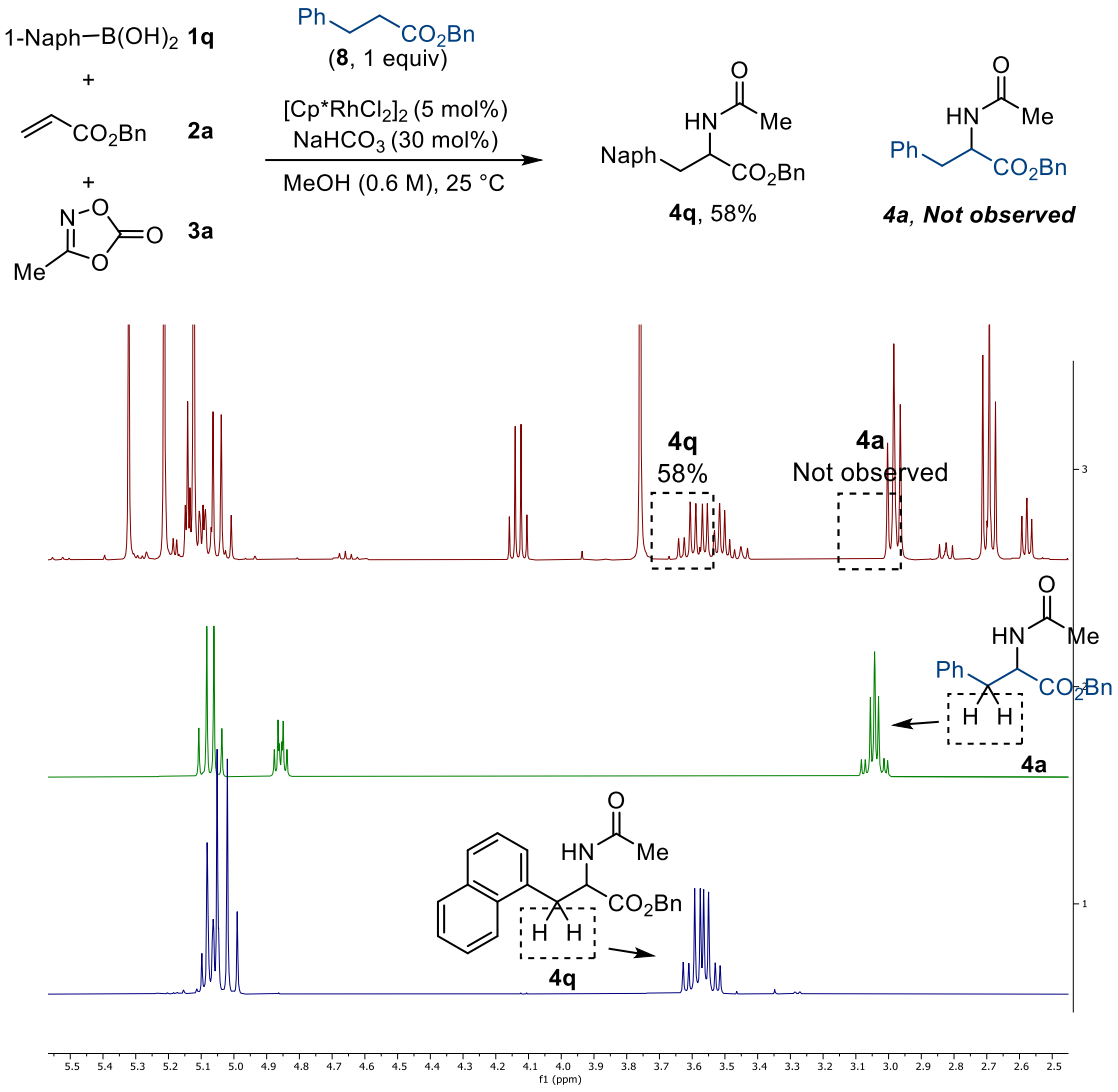
Reversibility of β-hydride elimination



Benzyl cinnamate **7** was prepared according to literature procedures.[9] $[Cp^*RhCl_2]_2$ (0.0050 mmol, 5 mol%) and sodium bicarbonate (0.03 mmol, 30 mol%), and naphthalene-1-boronic acid **1q** (0.25 mmol, 2.5 equiv) were measured in a 0.5-dram vial with a magnetic stir bar. In a separate vial, benzyl cinnamate **7** (0.1 mmol, 1 equiv) was dissolved 0.10 mL of MeOH and transferred to the first vial. It was rinsed with an additional 0.07 mL of MeOH and transferred again to the first vial. Sequentially benzyl acrylate **2a** (0.3 mmol, 3 equiv) and dioxazolone **3a** (0.1 mmol, 1 equiv) were added to the reaction mixture using a micropipette. The reaction mixture was then stirred at room temperature for 16 hours. After the completion of the reaction, the solvent was removed by a rotary evaporator. Ethyl acetate was added to the residue and filtered through a short pad of celite and washed with ethyl acetate three times. The filtrate was concentrated by rotary

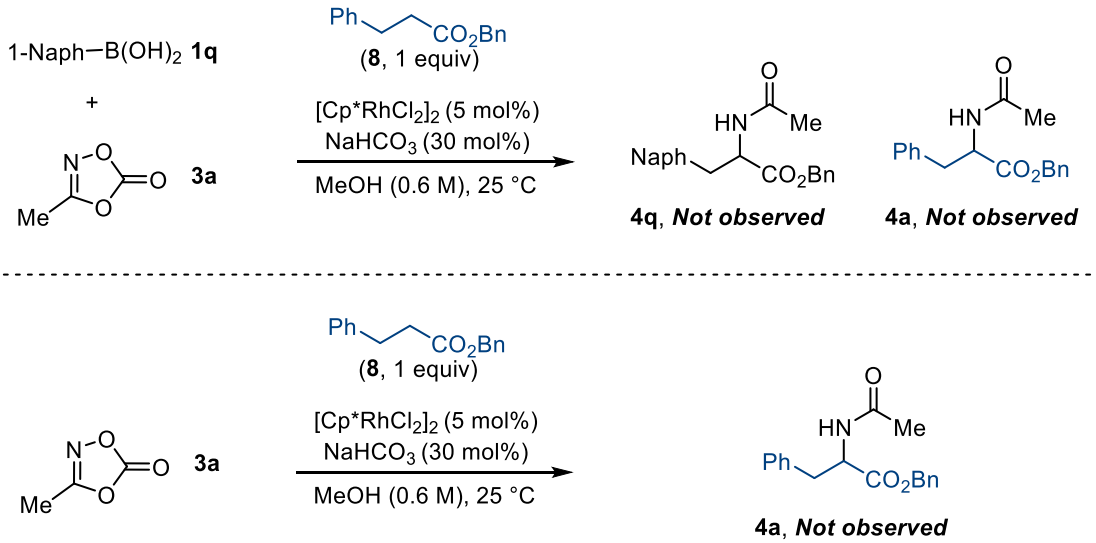
evaporator and a crude ^{1}H NMR spectrum was collected with 1,3,5-trimethoxybenzene as the internal standard).

Reversibility of proto-demetalation step



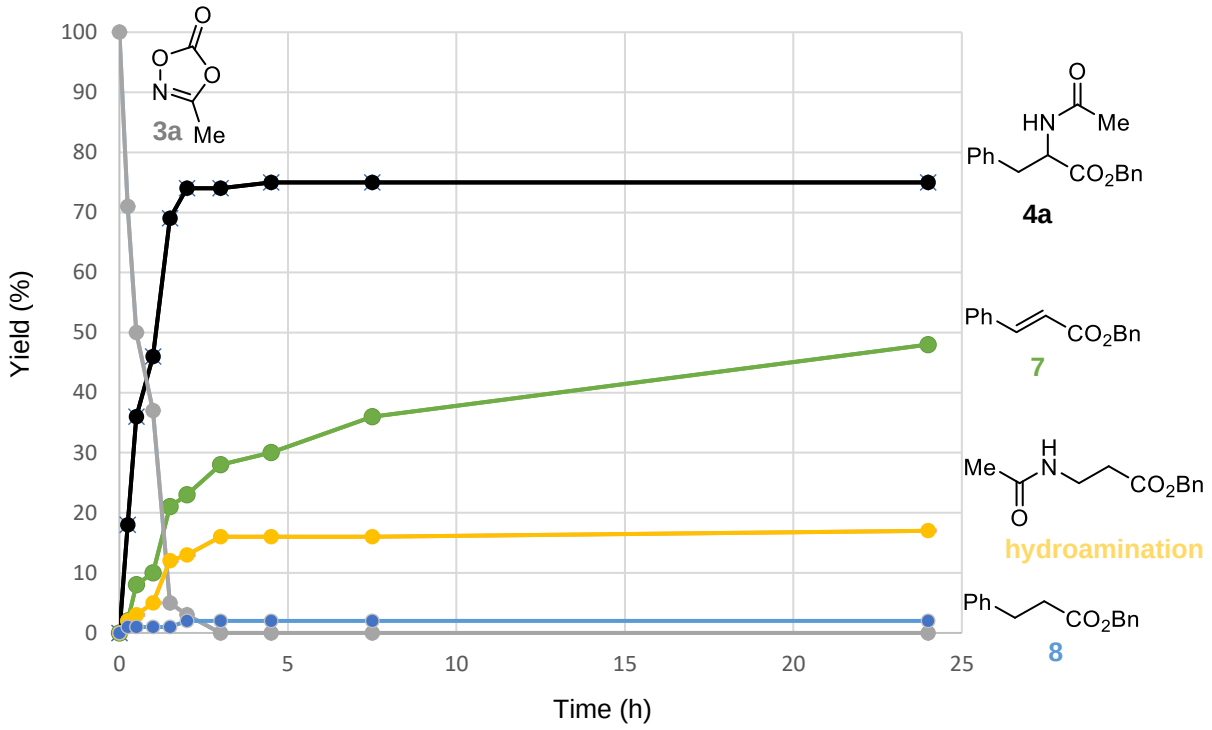
Benzyl 3-phenylpropanoate **8** was prepared according to literature procedures.[10] $[Cp^*RhCl_2]_2$ (0.0050 mmol, 5 mol%) and sodium bicarbonate (0.03 mmol, 30 mol%), and naphthalene-1-boronic acid **1q** (0.25 mmol, 2.5 equiv) were measured in a 0.5-dram vial with a magnetic stir bar. In a separate vial, Benzyl 3-phenylpropanoate **8** (0.1 mmol, 1 equiv) were dissolved 0.10 mL of MeOH and transferred to the first vial. It was rinsed with an additional 0.7 mL of MeOH and transferred again to the first vial. Sequentially benzyl acrylate **2a** (0.3 mmol, 3 equiv) and dioxazolone **3a** (0.1 mmol, 1 equiv) were added to the reaction mixture

using a micropipette. The reaction mixture was then stirred at room temperature for 16 hours. After the completion of the reaction, the solvent was removed by a rotary evaporator. Ethyl acetate was added to the residue and filtered through a short pad of celite and washed with ethyl acetate three times. The filtrate was concentrated by rotary evaporator and a crude ^{1}H NMR spectrum was collected with 1,3,5-trimethoxybenzene as the internal standard. While both reactions give the desired product (**4q**) from 1-naphthyl boronic acid (**2q**) in good yield, carboamination products (**4a**) from these side products (**7** or **8**) are not observed. This experiment suggests **7** and **8** are off-cycle side products that do not re-enter the catalytic cycle.



The same experiments were conducted without benzyl acrylate (**2a**) and without both naphthalene-1-boronic acid (**1q**) and benzyl acrylate (**2a**). As a result, carboamination products are not observed after the reaction, which again supports benzyl 3-phenylpropanoate (**8**) as an off-cycle side product.

Reaction progress monitoring



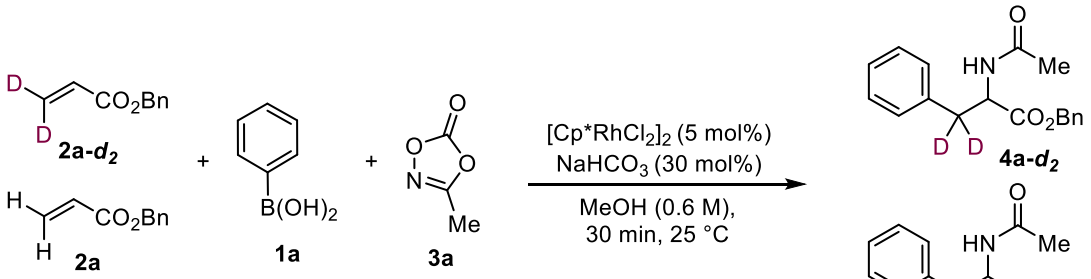
$[Cp^*RhCl_2]_2$ (0.0050 mmol, 5 mol%) and sodium bicarbonate (0.03 mmol, 30 mol%), and phenylboronic acid **1a** (0.25 mmol, 2.5 equiv) were measured in a 0.5-dram vial with a magnetic stir bar. In a separate vial, benzyl acrylate **2a** (0.3 mmol, 3 equiv) and dioxazolone **3a** (0.1 mmol, 1 equiv) were dissolved in 0.10 mL of MeOH. It was rinsed with an additional 0.07 mL of MeOH and transferred again to the first vial. 10 separate reactions were set up and each time the solvent was removed by rotary evaporator and ethyl acetate was added to the residue and filtered through a short pad of celite and washed with ethyl acetate three times. The filtrate was concentrated by rotary evaporator and a crude ^{1}H NMR spectrum was collected with 1,3,5-trimethoxybenzene as the internal standard.

Synthesis of benzyl acrylate-3,3-*d*$_2$ (2a-*d*$_2$)

Benzyl acrylate-3,3-*d*$_2$ (**2a-*d*$_2$**) was synthesized following literature[11] using (benzyloxycarbonylmethyl)triphenylphosphonium bromide and paraformaldehyde-*d*$_2$. To a solution of (benzyloxycarbonylmethyl)triphenylphosphonium bromide (10 mmol, 1 equiv) in a 2:1 mixture of Et_2O/H_2O (40 mL/20 mL), K_2CO_3 was added portionwise over 15 minutes. After stirring 24 hours at 35 °C, the layers were separated, and the water layer was extracted with Et_2O (10 mL) three times. The combined

organic layer was dried with $MgSO_4$ and filtered. To this solution, paraformaldehyde-d_2 (10.5 mmol, 1.05 equiv) was added and refluxed for 24 hours. After careful removal of the solvent, the crude material was purified by column chromatography using pentane and Et_2O. Yield: 48%, colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 5H), 6.18 (bs, 1H), 5.22 (s, 2H).

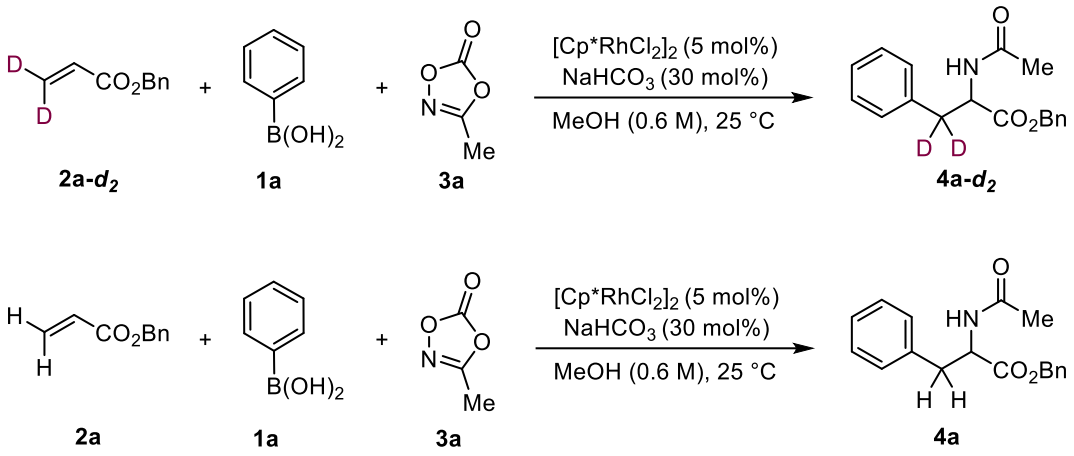
Intermolecular competition KIE



K_H/K_D = 0.72, inversed secondary KIE

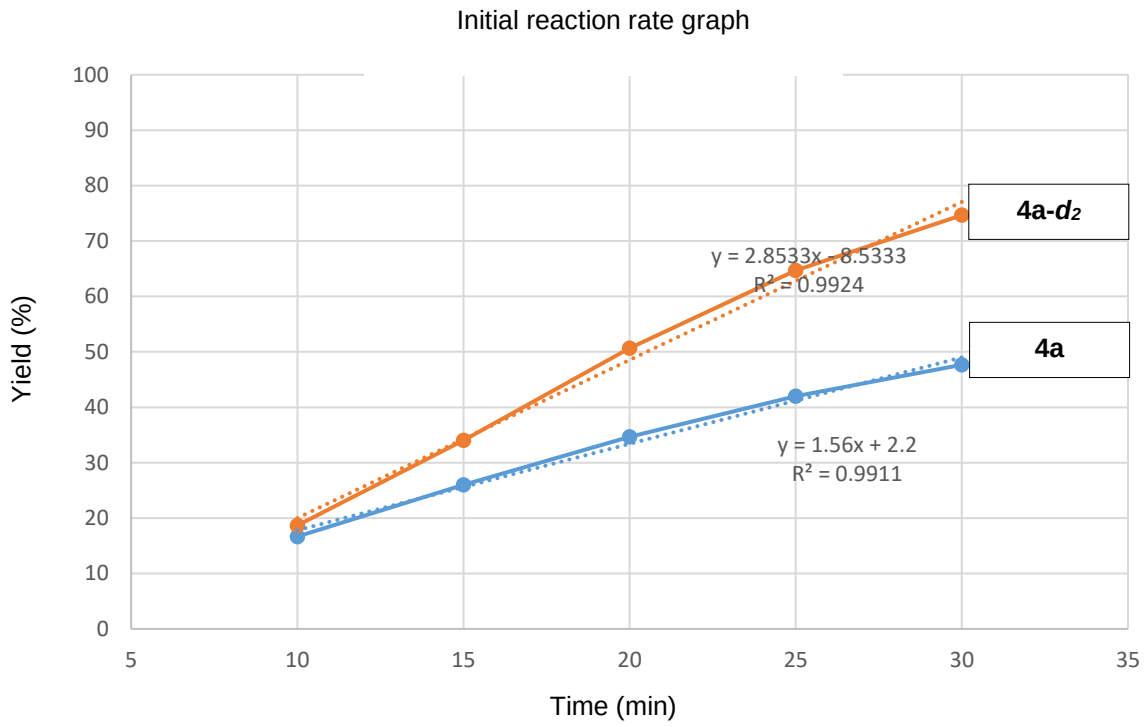
$[Cp^*RhCl_2]_2$ (0.010 mmol, 5 mol%), sodium bicarbonate (0.06 mmol, 30 mol%), and phenylboronic acid **1a** (0.50 mmol, 2.5 equiv) were measured in a 1-dram vial with a magnetic stir bar. In a separate vial, **2a** (0.15 mmol, 1.5 equiv) and **2a-*d*$_2$** (0.15 mmol, 1.5 equiv) were dissolved in 0.20 mL of MeOH containing 1,3,5-trimethoxybenzene as standard and transferred to the first vial. It was rinsed with an additional 0.13 mL of MeOH and transferred again to the first vial. After the addition of dioxazolone **3a** (0.20 mmol, 1 equiv), the reaction mixture was stirred at room temperature for 30 min. 20 uL aliquot was taken and diluted with 0.5 mL of MeCN-d_3 then analyzed by ^{1}H NMR. The KIE value was calculated based on the area of the 4.92 ppm (contribution from both molecules, **4a** and **4a-*d*$_2$**) and at 3.12 ppm (contribution solely from **4a**). The experiment was repeated three times and an average KIE value of 0.72 indicates $sp^2 \rightarrow sp^3$ hybridization change during the turnover limiting step, which suggests alkene migratory insertion as the turnover limiting step of the reaction.

Intermolecular parallel KIE



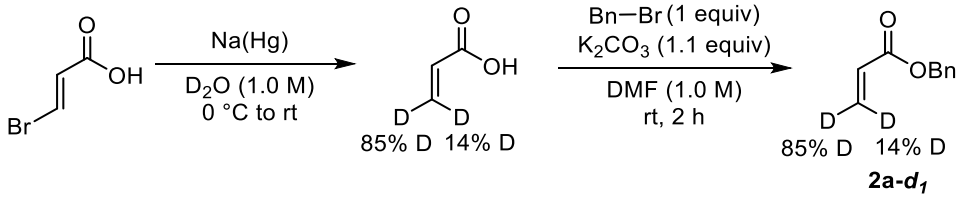
K_H/K_D = 0.55, inversed secondary KIE

KIE was measured from two separated reactions, one with benzyl acrylate (**2a**) containing two C-H bonds and benzyl acrylate-3,3-*d*$_2$ (**2a-*d*$_2$**) containing two C-D bonds. [Cp*RhCl$_2$]$_2$ (0.010 mmol, 5 mol%), sodium bicarbonate (0.06 mmol, 30 mol%), and phenylboronic acid **1a** (0.50 mmol, 2.5 equiv) were measured in a 1-dram vial with a magnetic stir bar. In a separate vial, **2a** (or **2a-*d*$_2$**) (0.60 mmol, 3 equiv) were dissolved in 0.20 mL of MeOH containing 1,3,5-trimethoxybenzene as standard and transferred to the first vial. It was rinsed with an additional 0.13 mL of MeOH and transferred again to the first vial. Dioxazolone **3a** (0.20 mmol, 1 equiv) was added to the reaction mixture using a micropipette and the reaction mixture was stirred at room temperature. To monitor the reaction progress, 20 uL aliquot was taken every 5 min and diluted with 0.5 mL of MeCN-*d*$_3$. KIE value was calculated by comparing the initial reaction rate (slope) of each reaction (repeated 3 times each) by using ^{1}H NMR. Observed inversed secondary KIE (K_H/K_D) value of 0.55 suggests $sp^2 \rightarrow sp^3$ hybridization change occurs during the turnover limiting step.



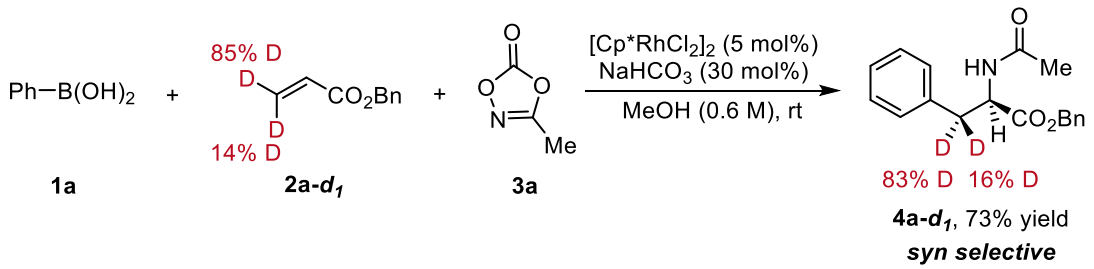
Syn addition of alkenes

Synthesis of benzyl acrylate-3-*d*$_1$ (2a-*d*$_1$)

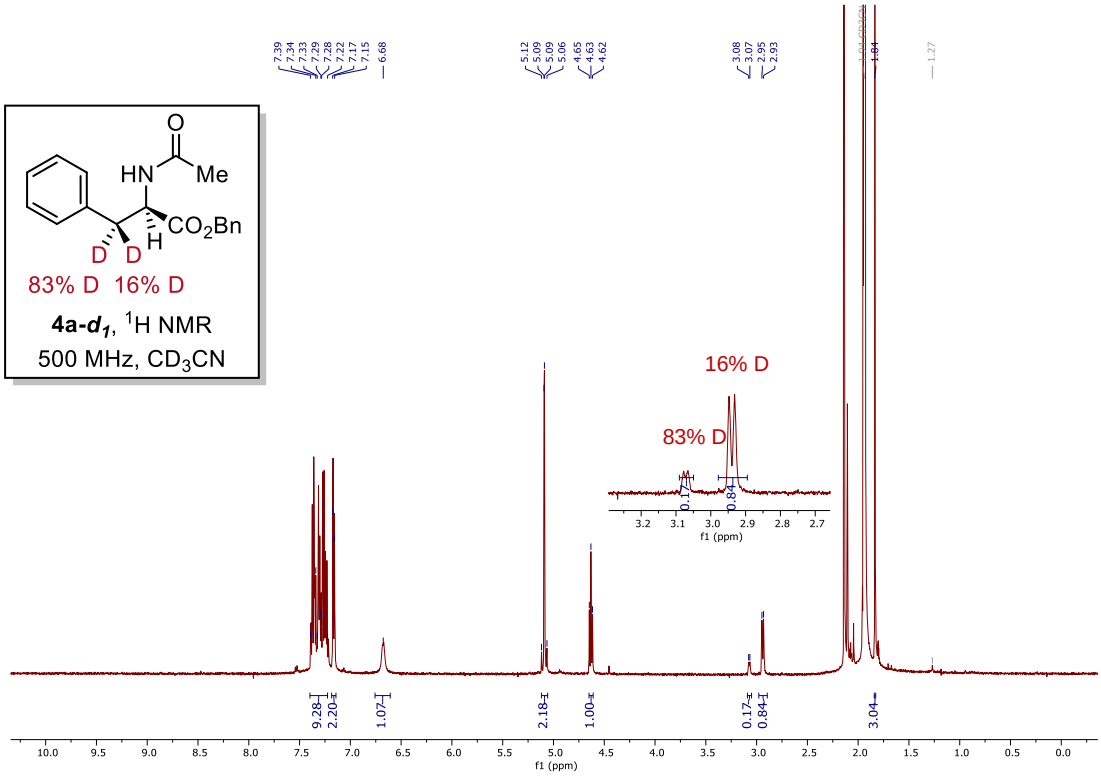


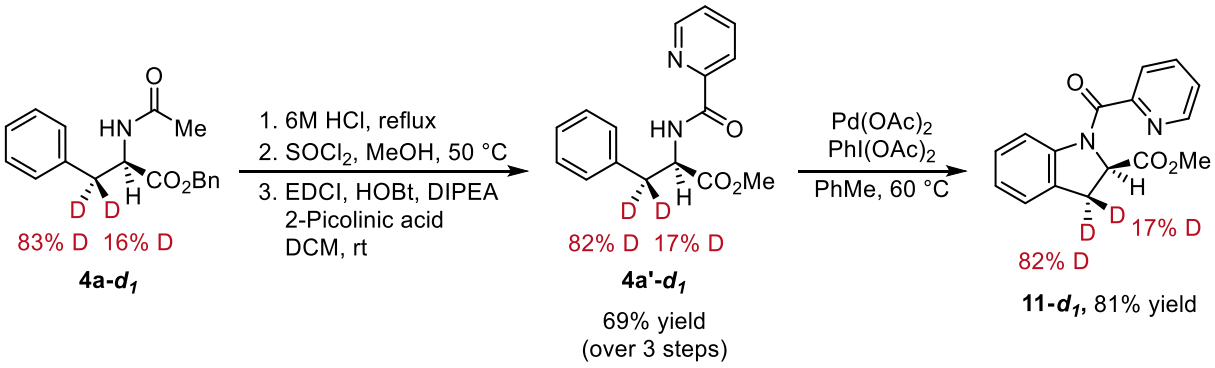
(*E*)-3-bromoacrylic acid was synthesized following literature.[12] To a solution of (*E*)-3-bromoacrylic acid (1.0 g, 6.62 mmol) in D_2O (1.0 M), 5.0 g of 20% sodium amalgam was added as one portion at 0 °C. After stirring 5 min at 0 °C for 5 min, the reaction mixture was warmed to room temperature and stirred additional 30 min. The reaction mixture was decanted and washed with water. The reaction mixture was acidified to pH ≈ 1 with 6 M HCl, then extracted with diethyl ether 3 times. The combined organic layer was washed with brine and dried over $MgSO_4$ and solvent was removed by a rotary evaporator. (*E*)-acrylic-3-*d* acid was used without further purification (around 20% of over reduction product was observed). To a mixture of K_2CO_3 (1.1 equiv) and benzyl bromide (1 equiv) in DMF (1.0 M), (*E*)-acrylic-3-*d* acid was added dropwise at room temperature. After stirring for two hours at room temperature, the reaction mixture was diluted

with diethyl ether and washed with water and brine. The organic layer was dried with $MgSO_4$ and concentrated. The crude material was purified by column chromatography using pentane and diethyl ether as eluent. **2a-*d*$_1$**. Yield: 20% (over two steps). Colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 5H), 6.44 (d, J = 17.3 Hz, 0.86H), 6.17 (dt, J = 17.2, 1.5 Hz, 1H), 5.84 (d, J = 10.5 Hz, 0.15H).

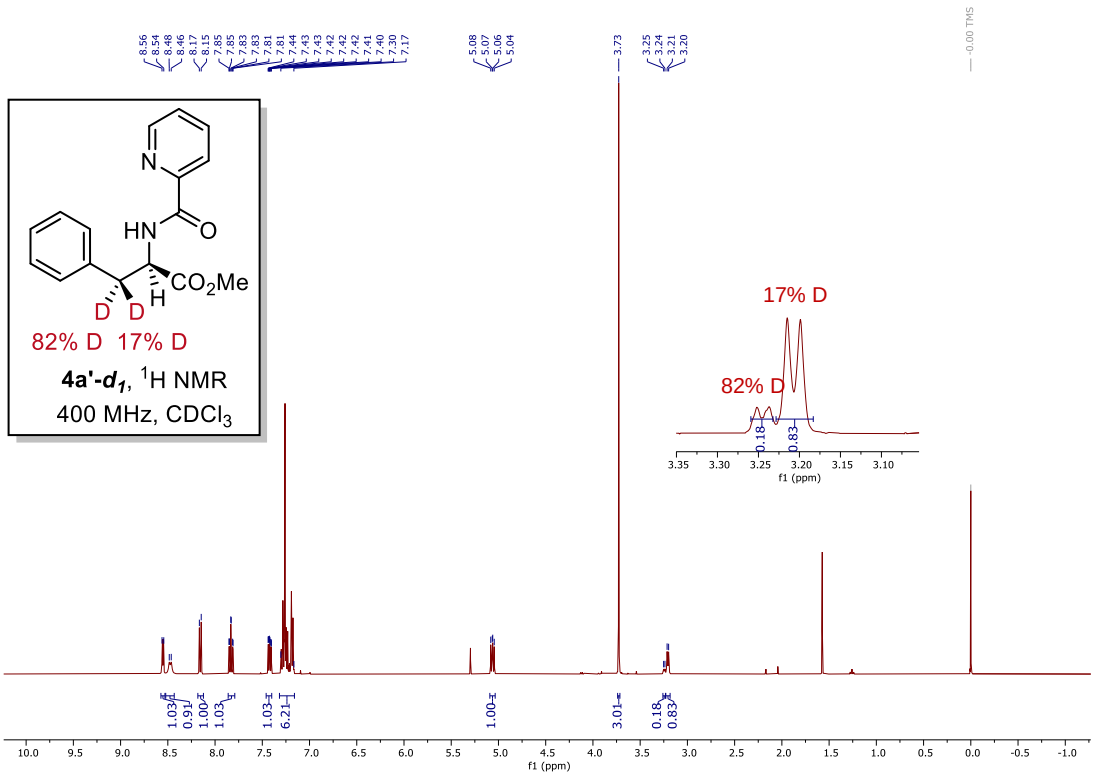


To a solution of $[Cp^*RhCl_2]_2$ (0.05 mmol, 5 mol%), sodium bicarbonate (0.30 mmol, 30 mol%), and phenylboronic acid **1a** (2.5 mmol, 2.5 equiv) in MeOH (1.7 mL, 0.6 M), **2a-*d*$_1$** (3.0 mmol, 3.0 equiv) and **3a** (1.0 mmol, 1 equiv) were added at room temperature and stirred overnight. The volatiles were removed by rotary evaporator and ethyl acetate was added and filtered through short pad of celite. After removing solvent using rotary evaporator, the crude material was purified by column chromatography using ethyl acetate and hexane as eluent to obtain **4a-*d*$_1$**. Yield: 73%, white solid. **^{1}H NMR** (500 MHz, CD_3CN) δ 7.40 – 7.22 (m, 8H), 7.18 – 7.14 (m, 2H), 6.67 (s, 1H), 5.12 – 5.06 (m, 2H), 4.63 (t, J = 7.8 Hz, 1H), 3.07 (d, J = 6.1 Hz, 0.17H), 2.94 (d, J = 8.0 Hz, 0.84H), 1.84 (s, 3H).

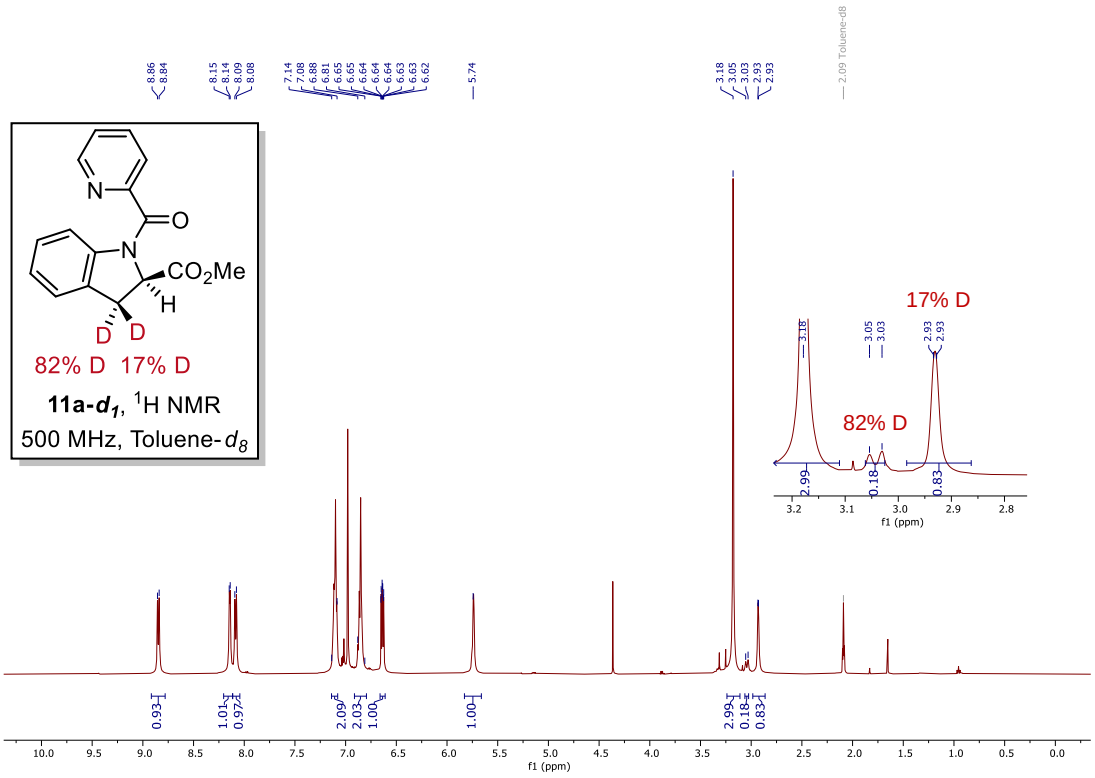




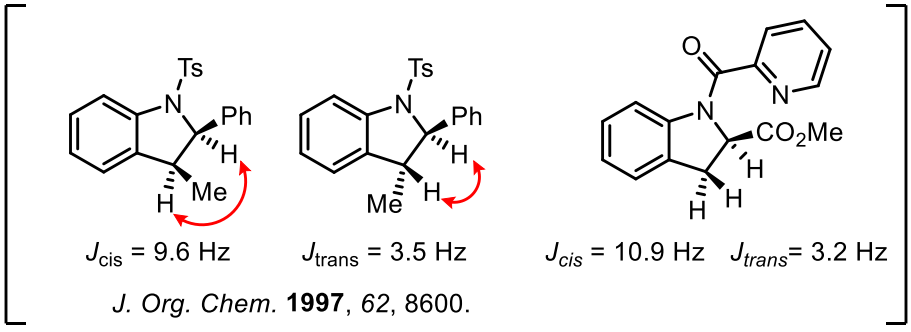
6 M HCl (0.1 M) was added to **4a-*d*$_1$** (1.38 mmol) and refluxed for 4 hours. After removing volatiles, diethyl ether was added, and the white solid was collected by filteration. The resulting solid was washed with diethyl ether and dried under high vacuum. The deprotected product was dissolved in MeOH (0.25 M) and $SOCl_2$ (1.5 equiv) was added dropwise at 0 °C. The reaction mixture was warmed to room temperature and heated at 50 °C for 3 hours. The volatiles were removed by a rotary evaporator and diethyl ether was added. After stirring for 10 min at 0 °C, the white solid was filtered and washed with diethyl ether to give crude deuterated phenylalanine methyl ester hydrochloride. The crude material (1 equiv) and 2-picolinic acid (1.1 equiv) were dissolved in DCM (0.2 M) and HOBt hydrate (1.1 equiv) and DIPEA (3.0 equiv) were added at room temperature. The reaction mixture was cooled to 0 °C and EDCI (1.1 equiv) was added. After stirring for 5 min, the reaction mixture was warmed to room temperature and stirred overnight. Water was added and extracted with DCM three times. The combined organic layer was washed with water and brine and dried with Na_2SO_4. After removing the solvent, the crude material was purified by column chromatography using ethyl acetate and hexane as eluent to obtain **4a'-*d*$_1$**. Yield: 69% (over three steps). White solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.55 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 8.47 (d, J = 8.4 Hz, 1H), 8.16 (dt, J = 7.8, 1.1 Hz, 1H), 7.83 (td, J = 7.7, 1.7 Hz, 1H), 7.42 (ddd, J = 7.6, 4.8, 1.3 Hz, 1H), 7.33 – 7.14 (m, 5H), 5.06 (dd, J = 8.4, 6.3 Hz, 1H), 3.73 (s, 3H), 3.24 (d, J = 5.8 Hz, 0.18H), 3.21 (d, J = 6.5 Hz, 0.83H).

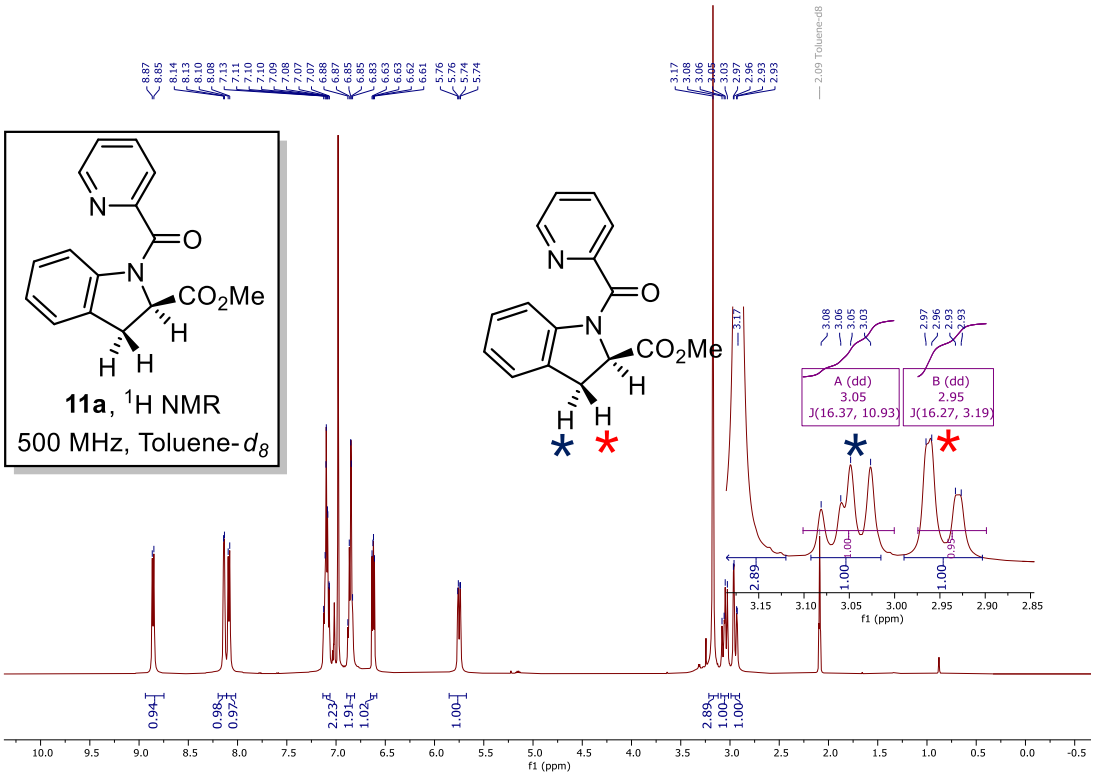


9a-*d*$_1$ was prepared following the literature.[13] In a 20 mL vial, $Pd(OAc)_2$ (2 mol%, 0.018 mmol) and $PhI(OAc)_2$ (2 equiv. 1.78 mmol) were measured in the glovebox. In a separate flask, **4a'-*d*$_1$** (1 equiv, 0.89 mmol) was dissolved in toluene (0.125 M) and transferred to the first vial. After purging with Ar for 10 min, the vial was sealed and heated at 60 °C for 24 hours. The reaction mixture was concentrated and purified by column chromatography using ethyl acetate and hexane as eluent. **11a-*d*$_1$**. Yield: 81%, white solid. **^{1}H NMR** (500 MHz, toluene-d_8) δ 8.85 (d, J = 8.2 Hz, 1H), 8.14 (d, J = 4.8 Hz, 1H), 8.09 (d, J = 7.9 Hz, 1H), 7.15 – 7.16 (m, 2H), 6.89 – 6.81 (m, 2H), 7.04 – 6.96 (m, 2H), 6.64 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 5.77 – 5.71 (m, 1H), 3.18 (s, 3H), 3.04 (d, J = 11.8 Hz, 0.18H), 2.93 (s, 0.83H).



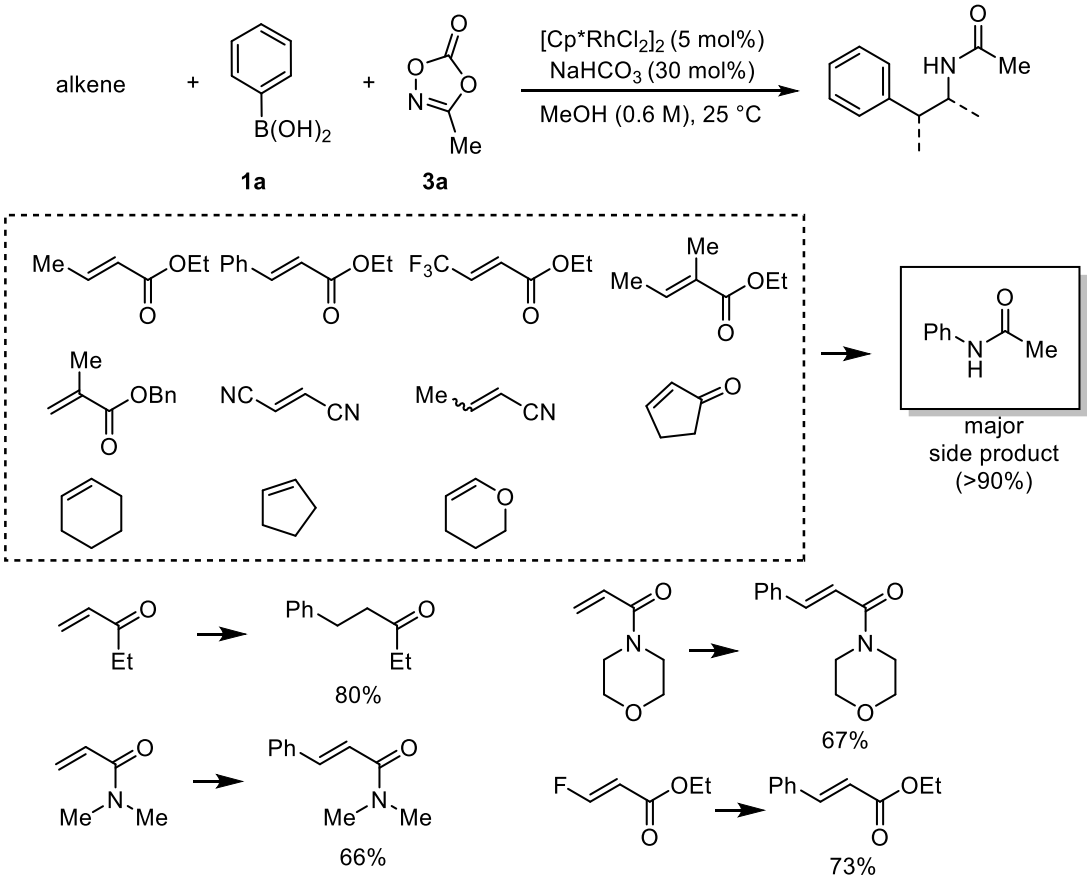
11a was synthesized from phenylalanine using same procedure described above. **11a**. White solid. **^{1}H NMR** (500 MHz, toluene-d_8) δ 8.86 (d, J = 8.2 Hz, 1H), 8.14 (d, J = 4.5 Hz, 1H), 8.09 (d, J = 7.9 Hz, 1H), 7.09 (td, J = 9.6, 7.8, 6.0 Hz, 2H), 6.89 – 6.81 (m, 2H), 6.62 (dd, J = 7.7, 4.8 Hz, 1H), 5.75 (dd, J = 10.9, 3.2 Hz, 1H), 3.17 (s, 3H), 3.05 (dd, J = 16.4, **10.9** Hz, 1H), 2.95 (dd, J = 16.3, **3.2** Hz, 1H). The relative stereochemistry was assigned based on the literature.[14] Benzylic proton with 10.9 Hz coupling constant was assigned as cis proton and proton with 3.2 Hz was assigned as trans proton which confirms the syn-carboamination of the reaction.



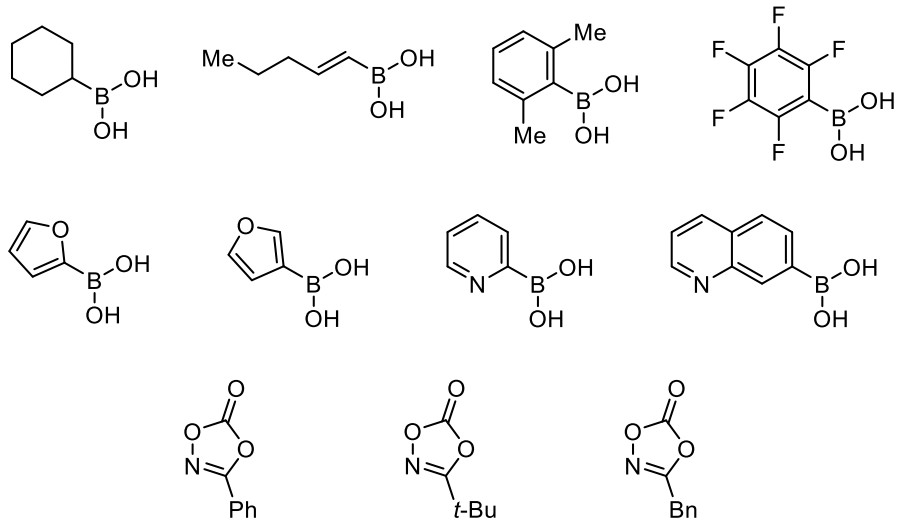

11a, 1H NMR
500 MHz, Toluene-d8
A (dd)
3.05
J(16.37, 10.93)
B (dd)
2.95
J(16.27, 3.19)
f1 (ppm)

7. Limitation

<Unsuccessful alkene coupling partners>



<Unsuccessful boronic acids and dioxazolones>



8. Reference

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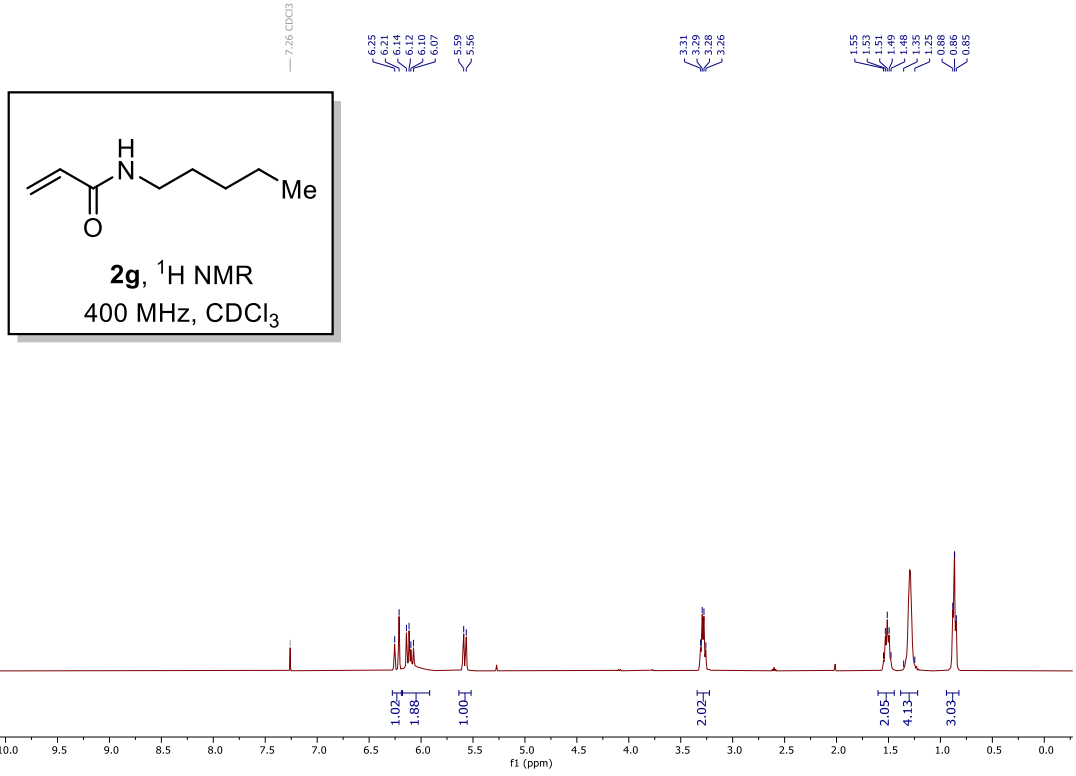
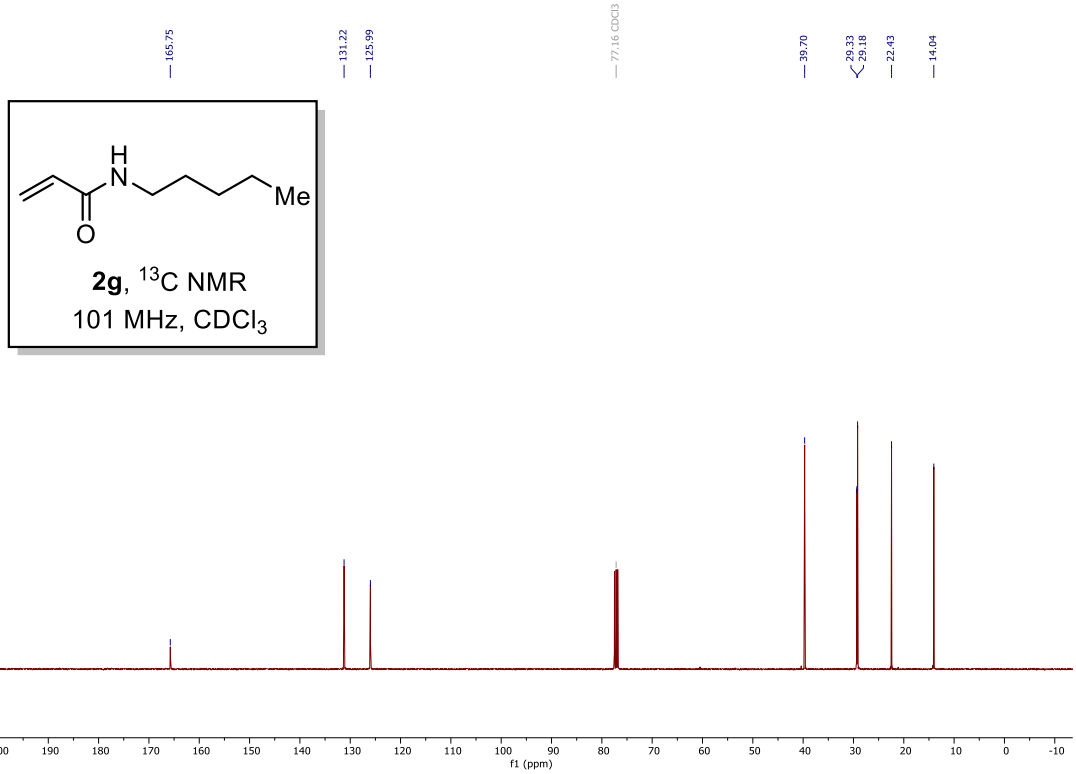
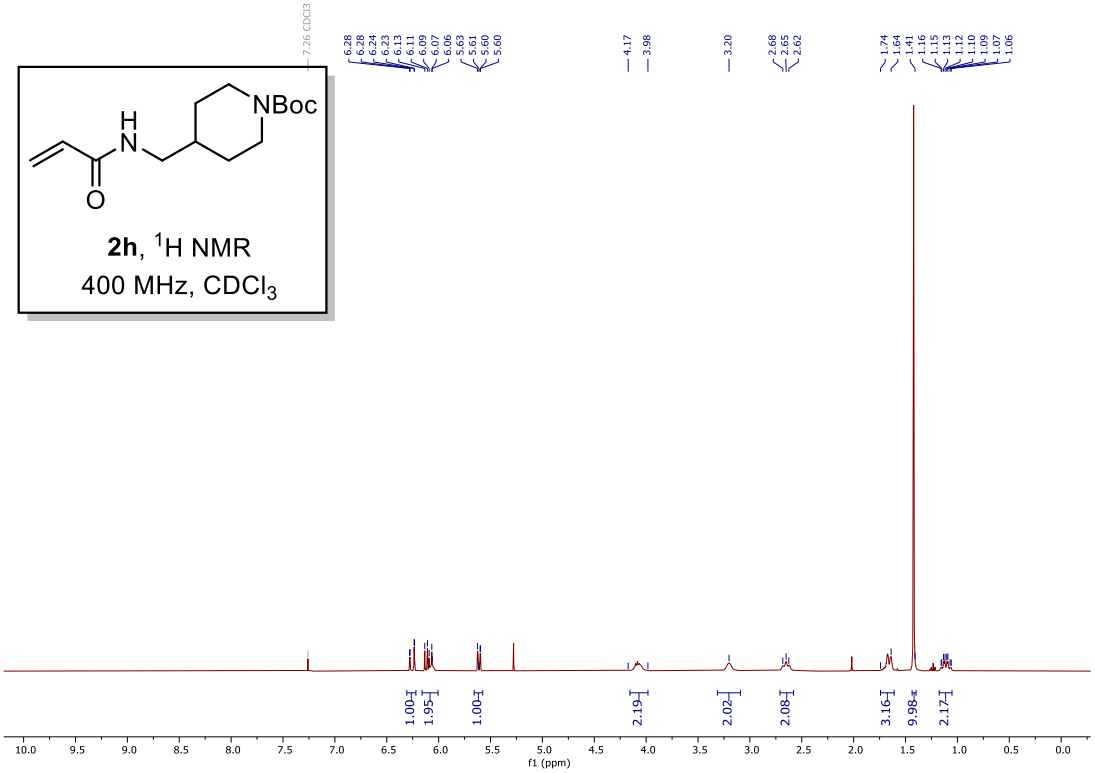
9. NMR Spectra






NBoc
H
N
O
2h, 1H NMR
400 MHz, CDCl3
7.26 CDCl3
6.28
6.28
6.24
6.23
6.13
6.11
6.09
6.07
6.06
5.63
5.61
5.60
5.60
4.17
3.98
3.20
2.68
2.65
2.62
1.74
1.64
1.41
1.16
1.15
1.13
1.12
1.10
1.09
1.07
1.06
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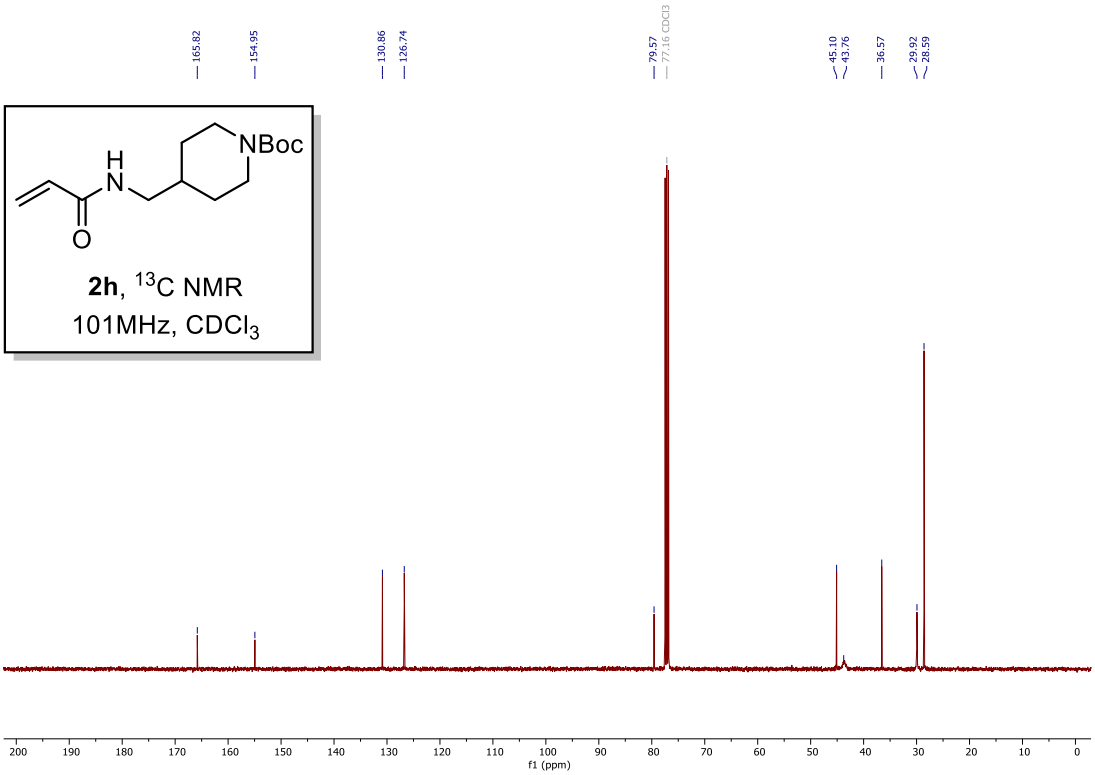
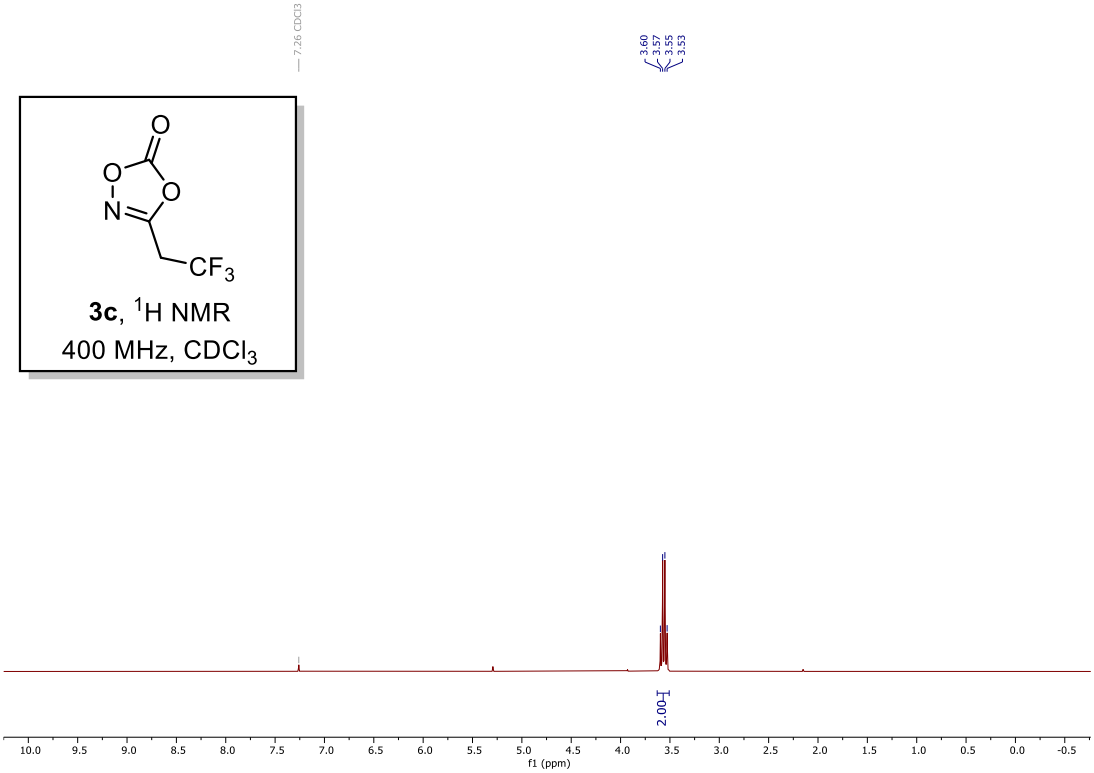
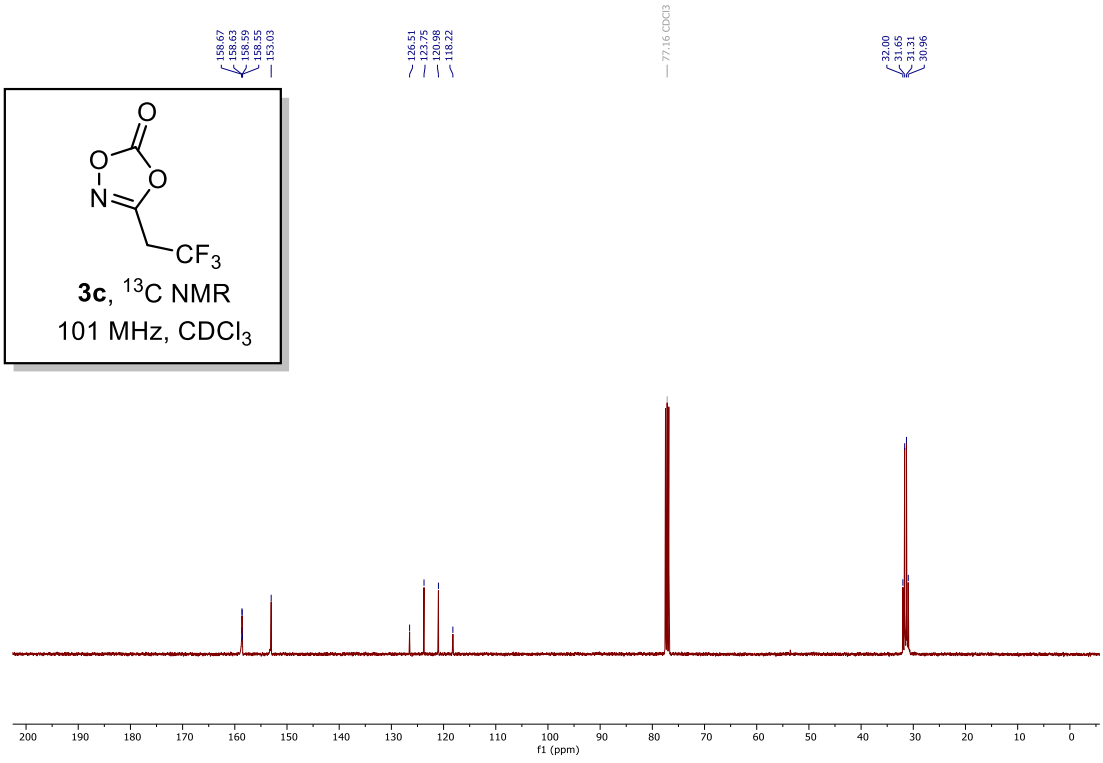
1.95
1.00
2.19
2.02
2.08
3.16
9.98
2.17
f1 (ppm)


NBoc
H
N
O
2h, 13C NMR
101MHz, CDCl3
165.82
154.95
130.86
126.74
79.57
77.16 CDCl3
45.10
43.76
36.57
29.92
28.59
f1 (ppm)

3c, ^{1}H NMR
400 MHz, $CDCl_3$

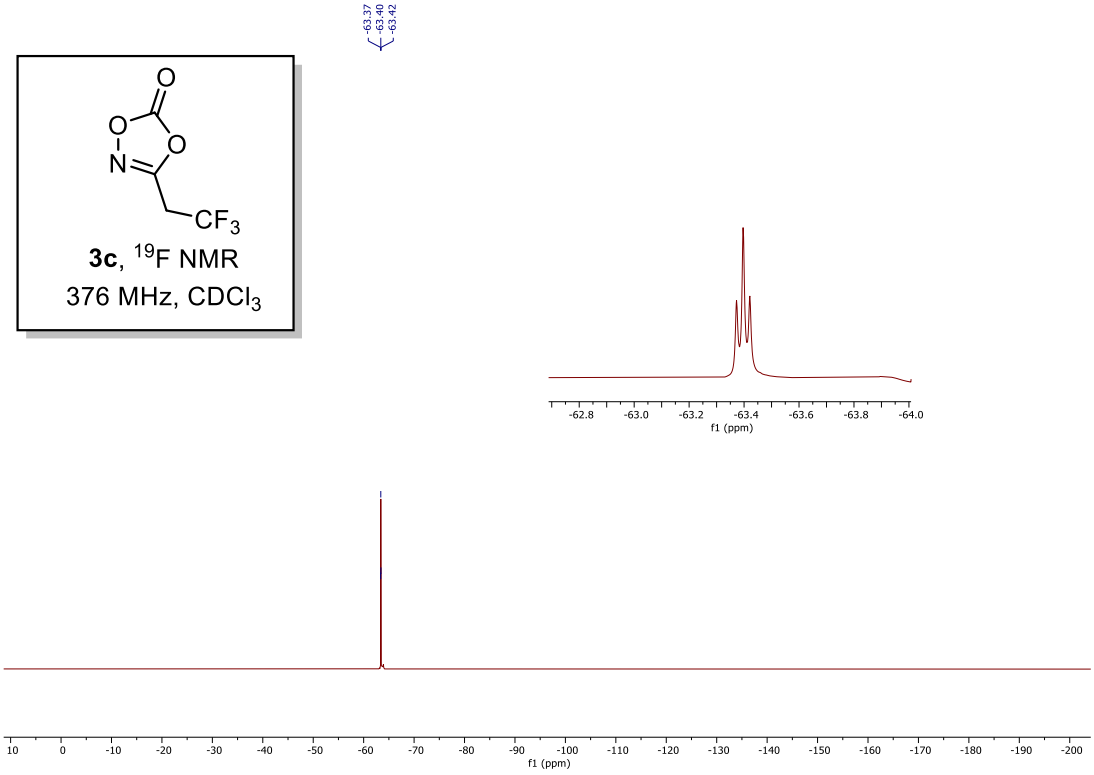


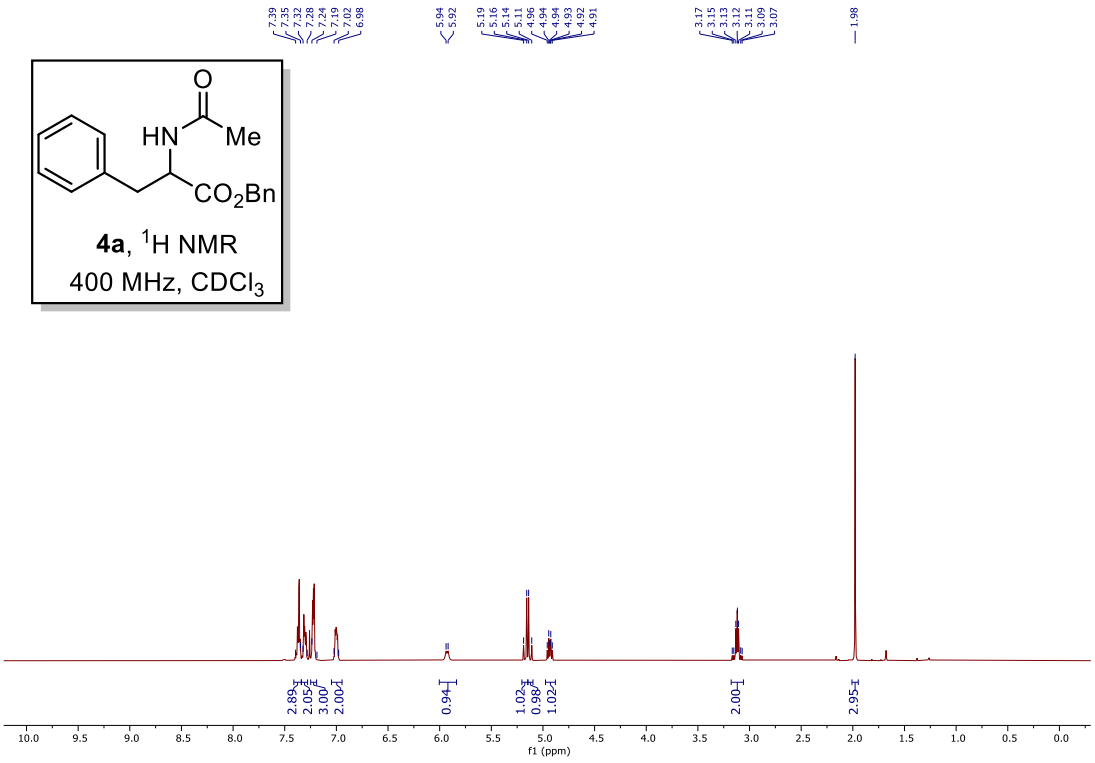
3c, ^{13}C NMR
101 MHz, $CDCl_3$



3c, ^{19}F NMR

376 MHz, $CDCl_3$




7.39
7.35
7.32
7.28
7.24
7.19
7.02
6.98
5.94
5.92
5.19
5.16
5.14
5.11
4.96
4.94
4.94
4.93
4.92
4.91
3.17
3.15
3.13
3.12
3.11
3.09
3.07
1.98
O
HN
Me
CO2Bn
4a, 1H NMR
400 MHz, CDCl3
2.89
2.05
3.00
2.00
0.94
1.02
0.98
1.02
2.00
2.95
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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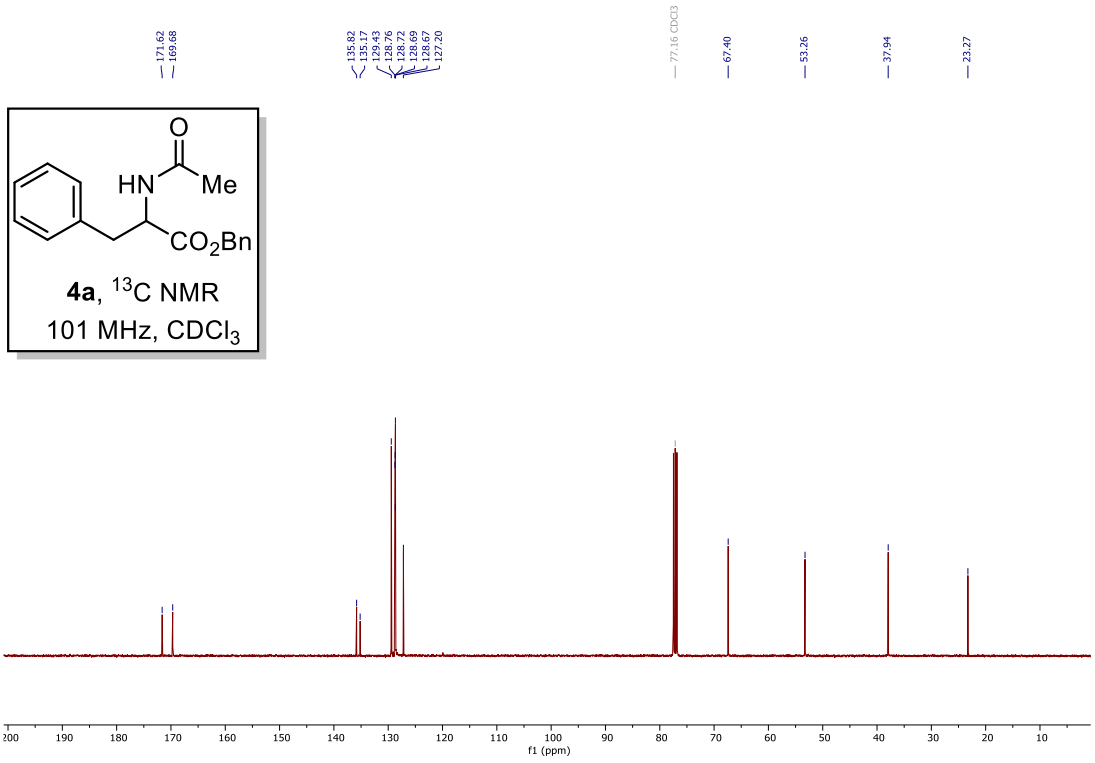
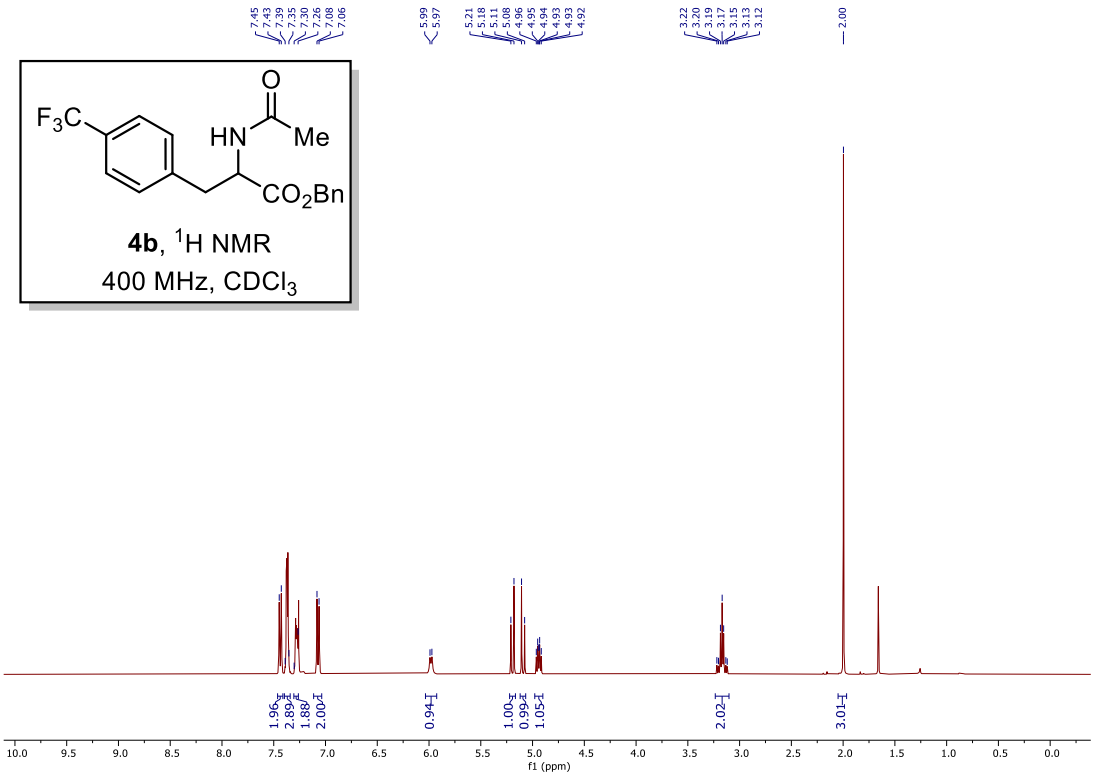
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


171.62
169.68
135.82
135.17
129.43
128.76
128.72
128.69
128.67
127.20
77.16 CDCl3
67.40
53.26
37.94
23.27
O
HN
Me
CO2Bn
4a, 13C NMR
101 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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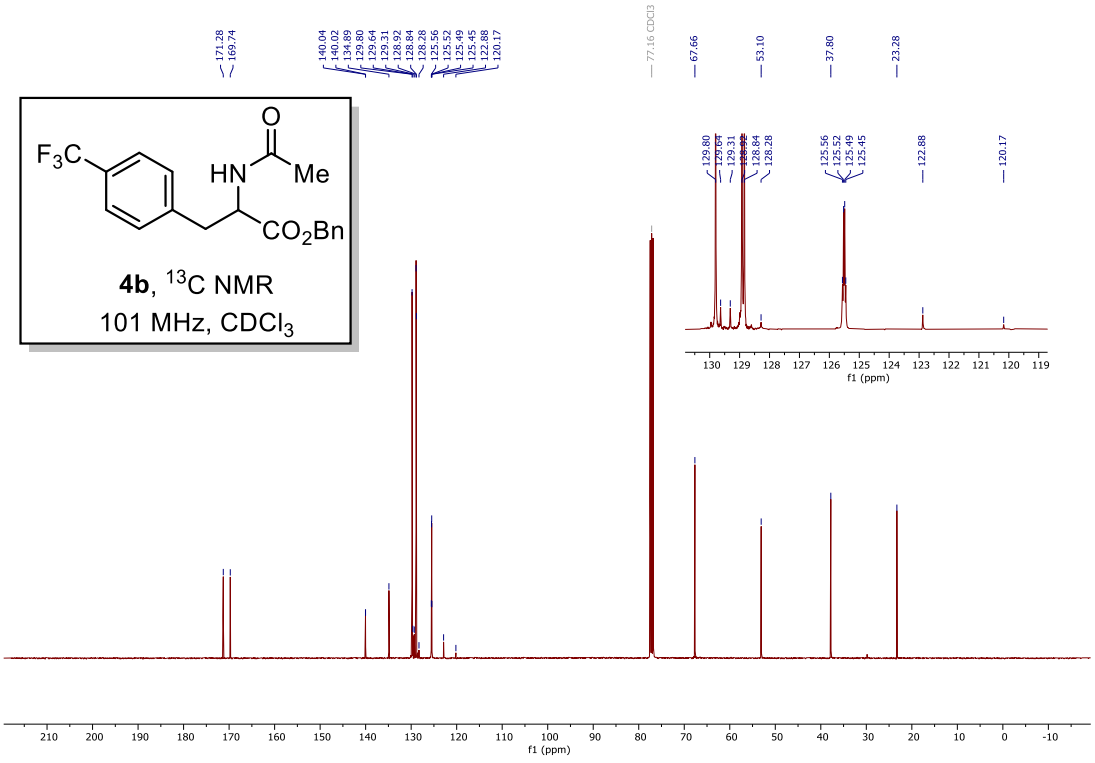
HN
O
Me
CO2Bn
4b, 1H NMR
400 MHz, CDCl3
f1 (ppm)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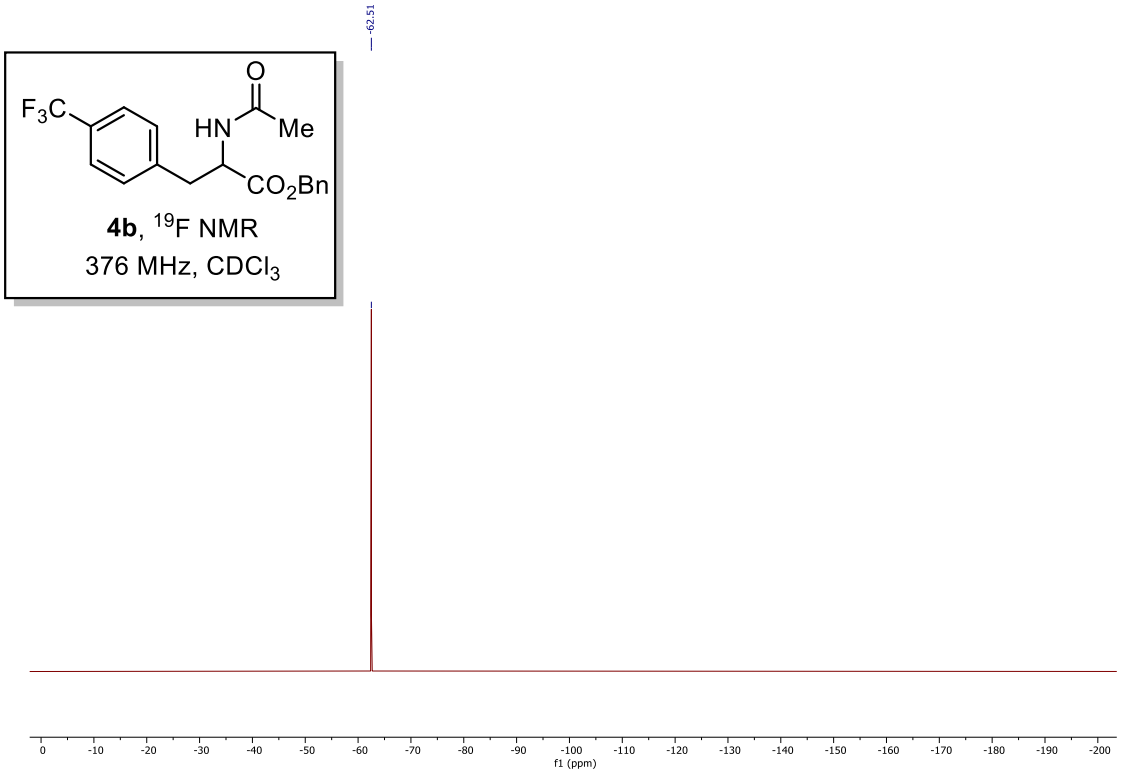
HN
O
Me
CO2Bn
4b, 13C NMR
101 MHz, CDCl3
f1 (ppm)


-62.51
F3C
HN
O
Me
CO2Bn
4b, 19F NMR
376 MHz, CDCl3
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
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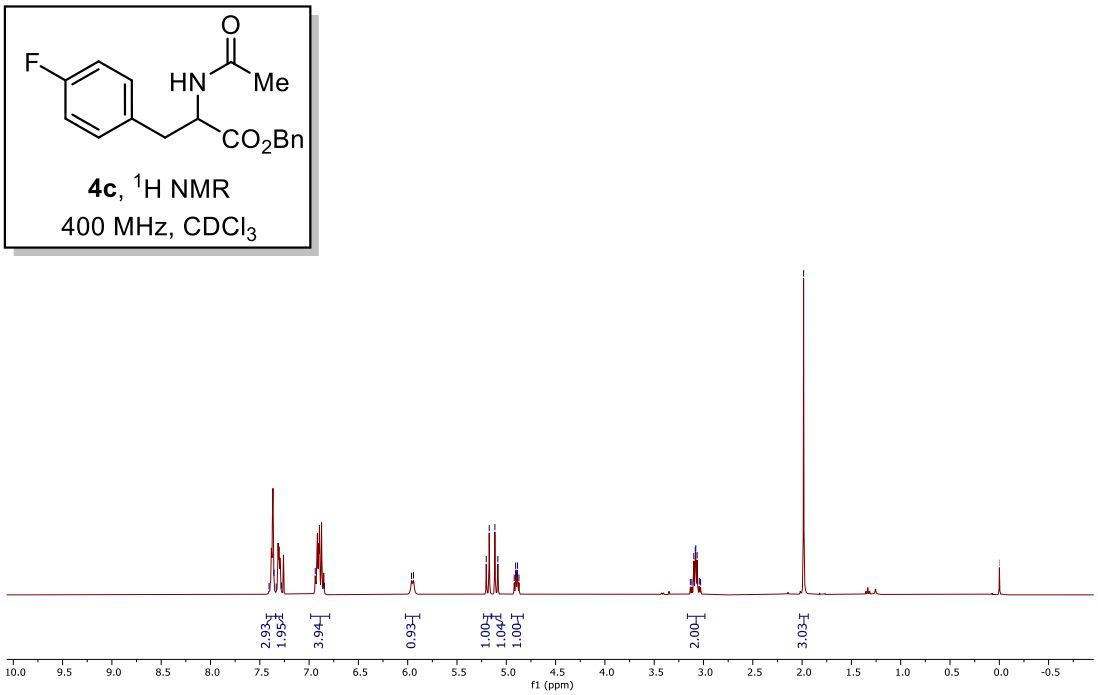
-190
-200
f1 (ppm)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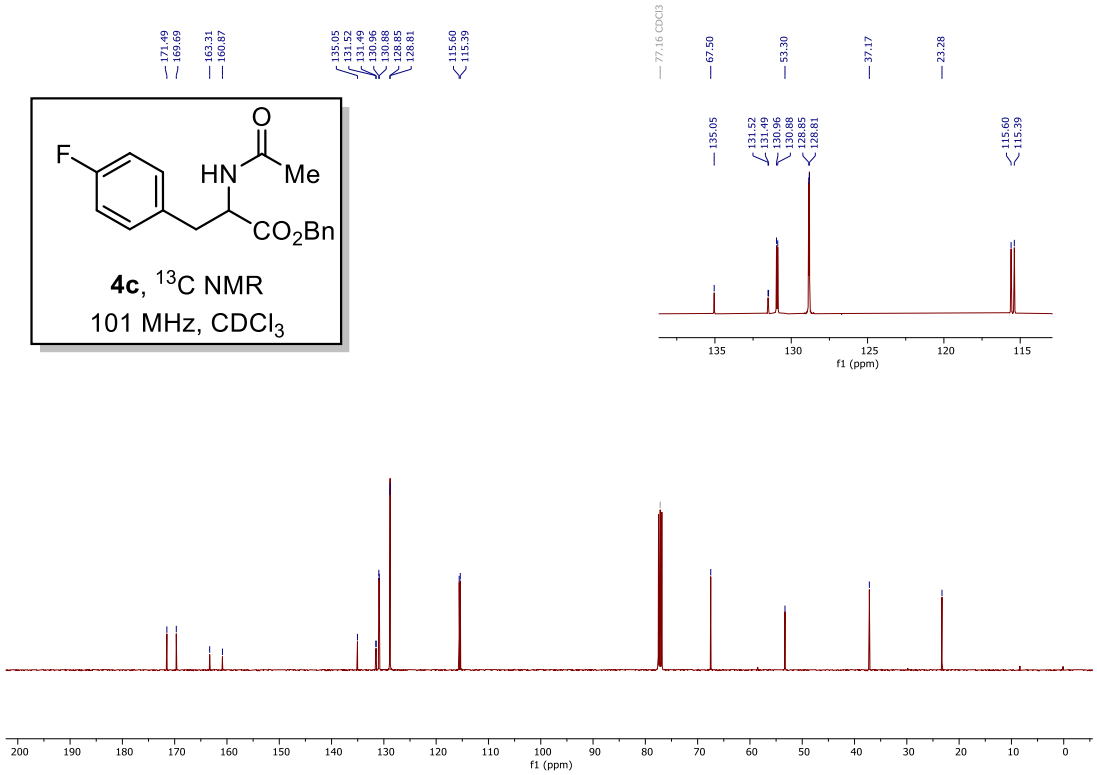
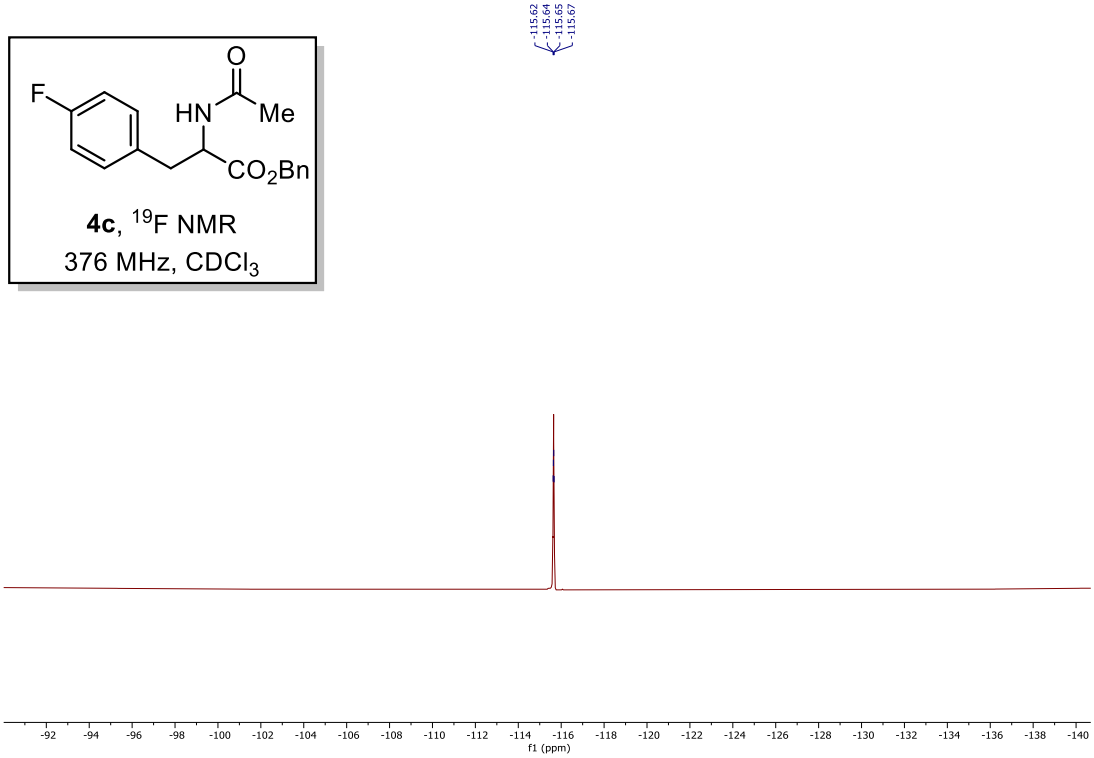
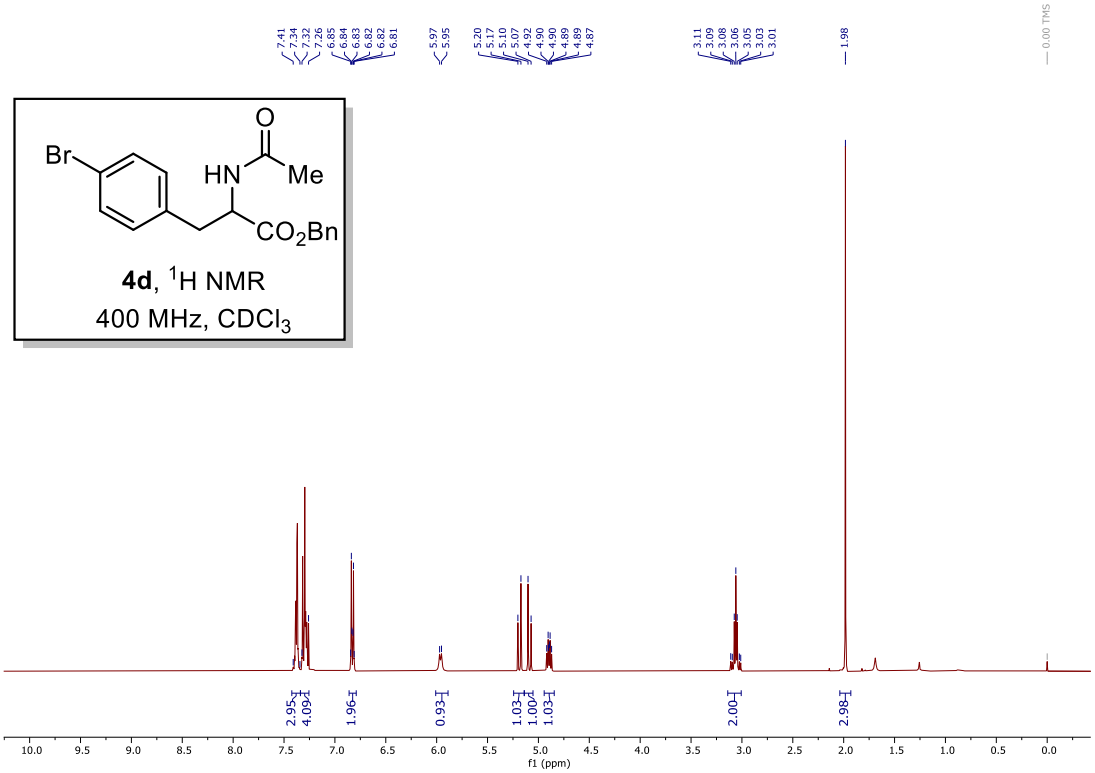
HN
O
Me
CO2Bn
4c, 1H NMR
400 MHz, CDCl3
f1 (ppm)


F
HN
O
Me
CO2Bn
4c, 13C NMR
101 MHz, CDCl3
f1 (ppm)

4c, ^{19}F NMR
376 MHz, $CDCl_3$

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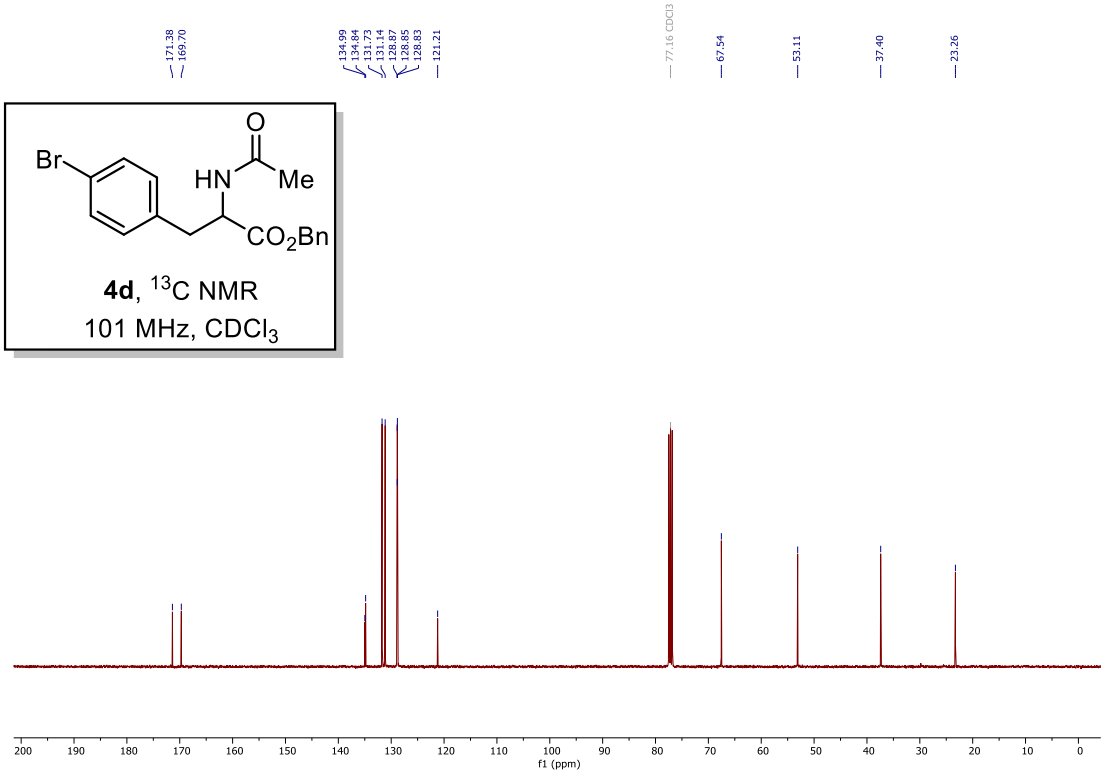
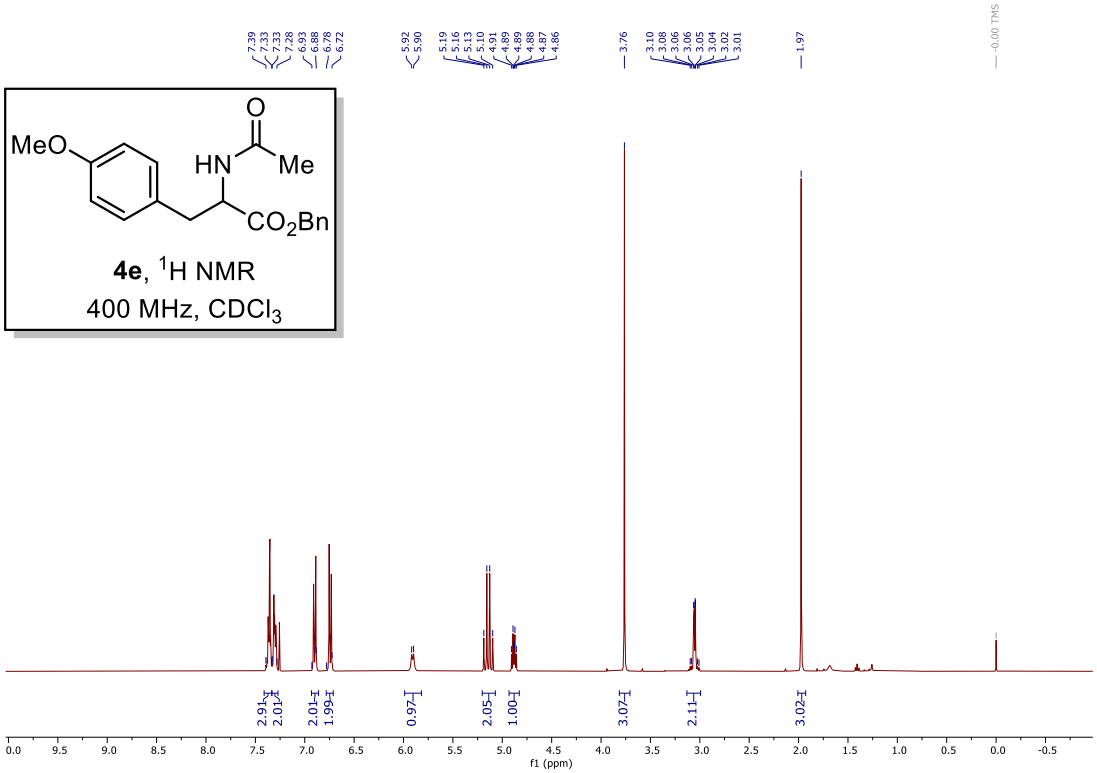
HN
O
Me
CO2Bn
4d, 1H NMR
400 MHz, CDCl3
f1 (ppm)


Br
HN
O
Me
CO2Bn
4d, 13C NMR
101 MHz, CDCl3
f1 (ppm)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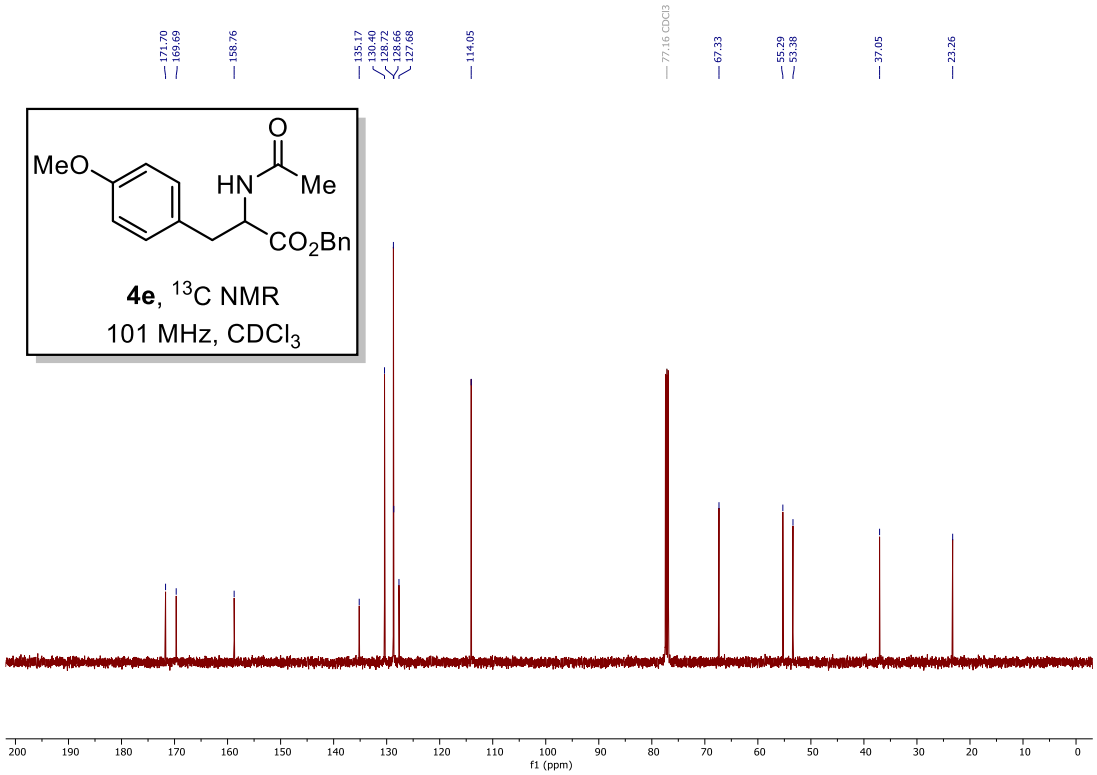
HN
O
Me
CO2Bn
4e, 1H NMR
400 MHz, CDCl3
f1 (ppm)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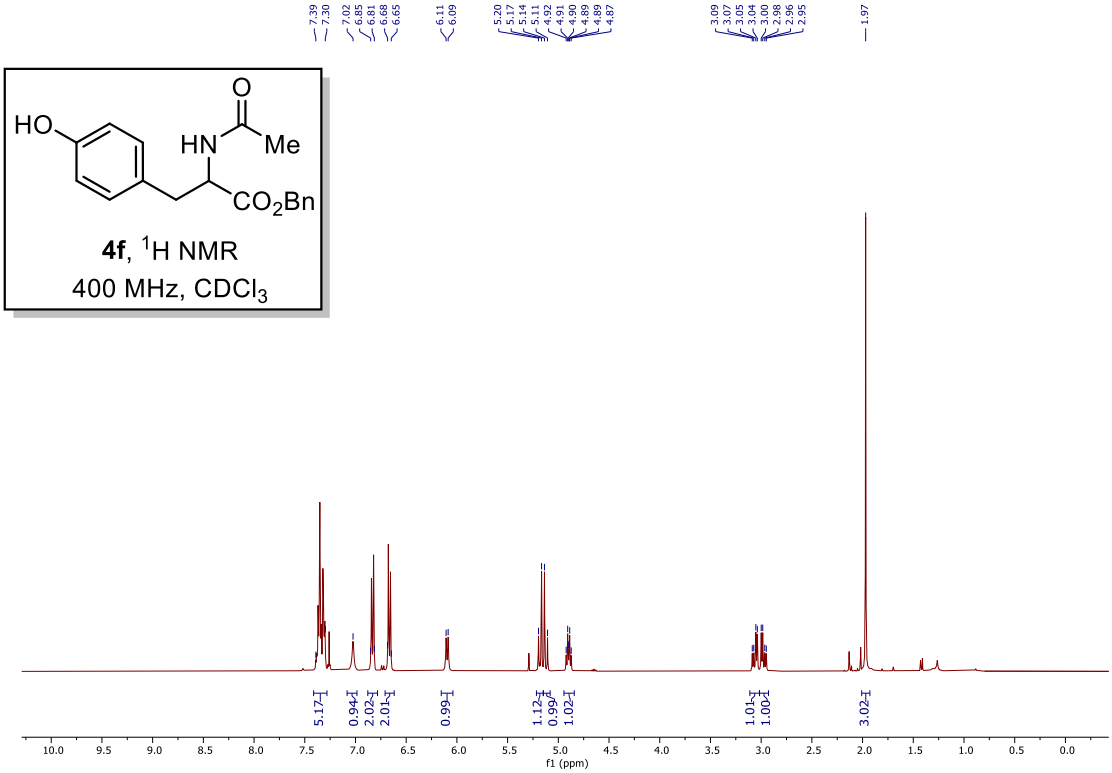
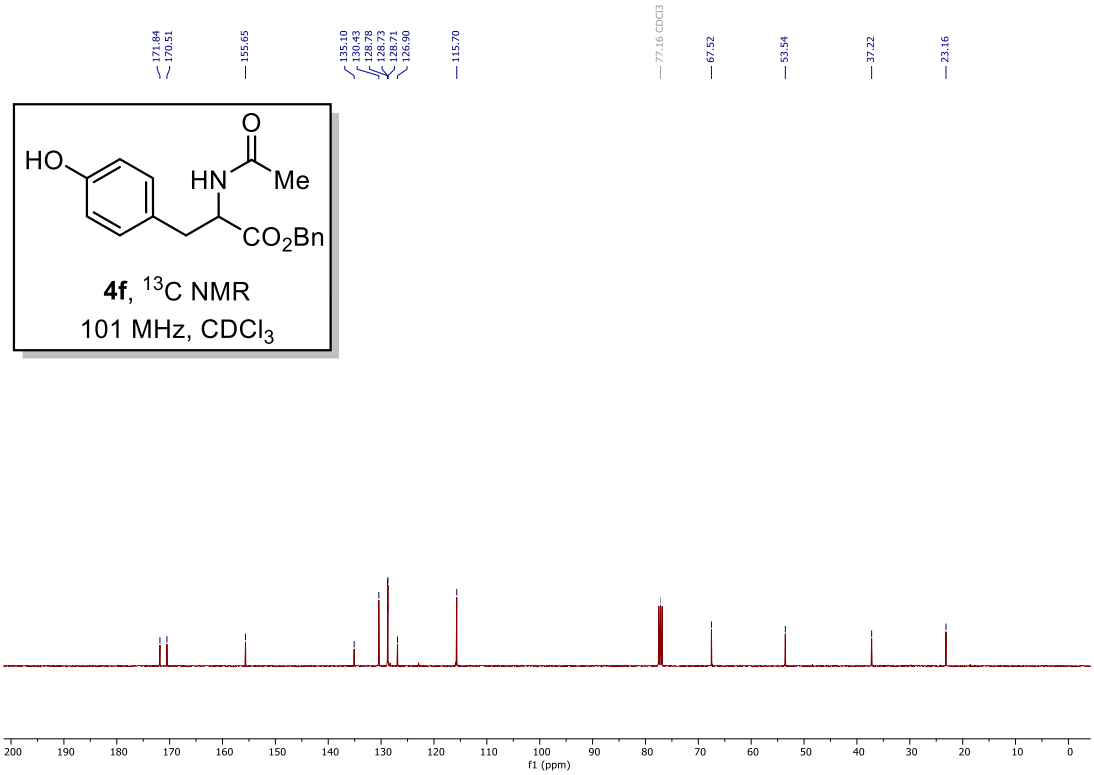
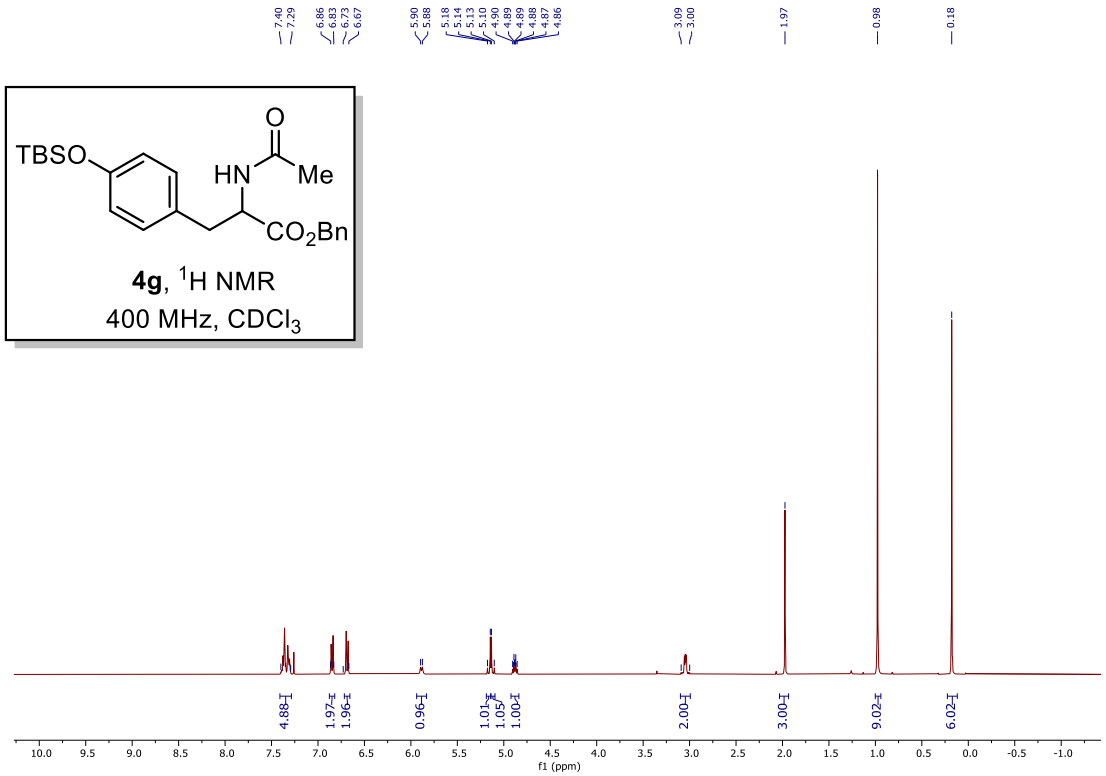
HN
O
Me
CO2Bn
4e, 13C NMR
101 MHz, CDCl3
f1 (ppm)

4f, ^{1}H NMR
400 MHz, $CDCl_3$



4f, ^{13}C NMR
101 MHz, $CDCl_3$

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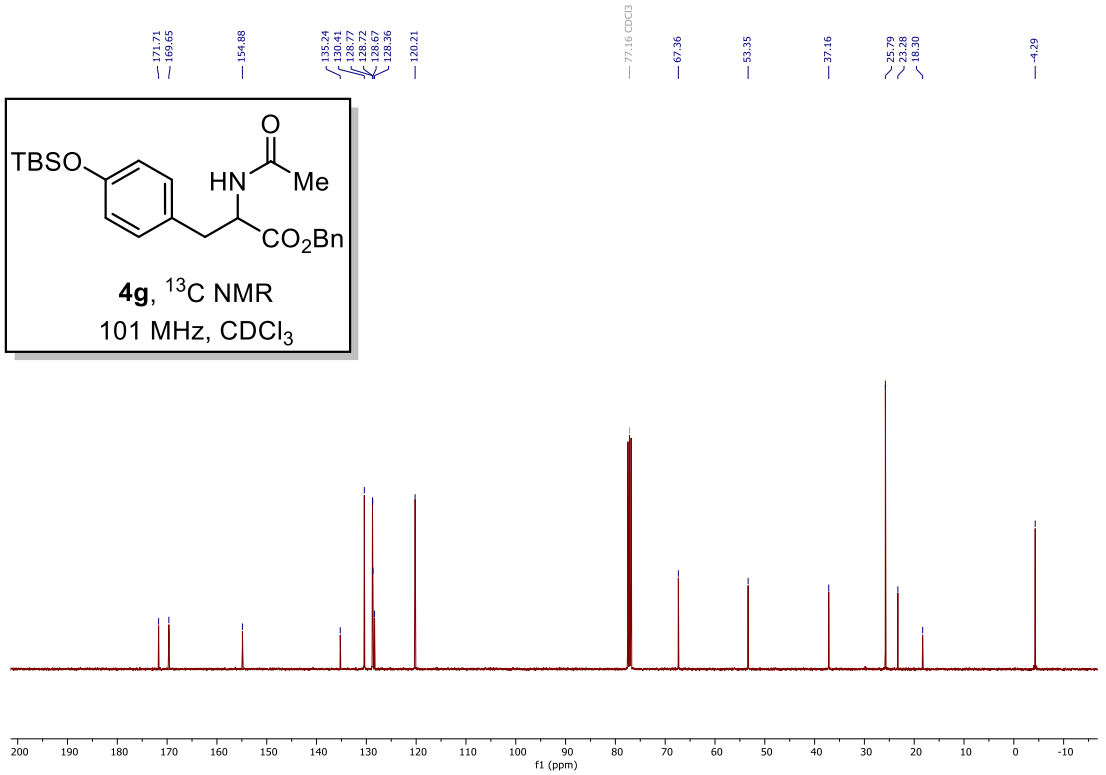
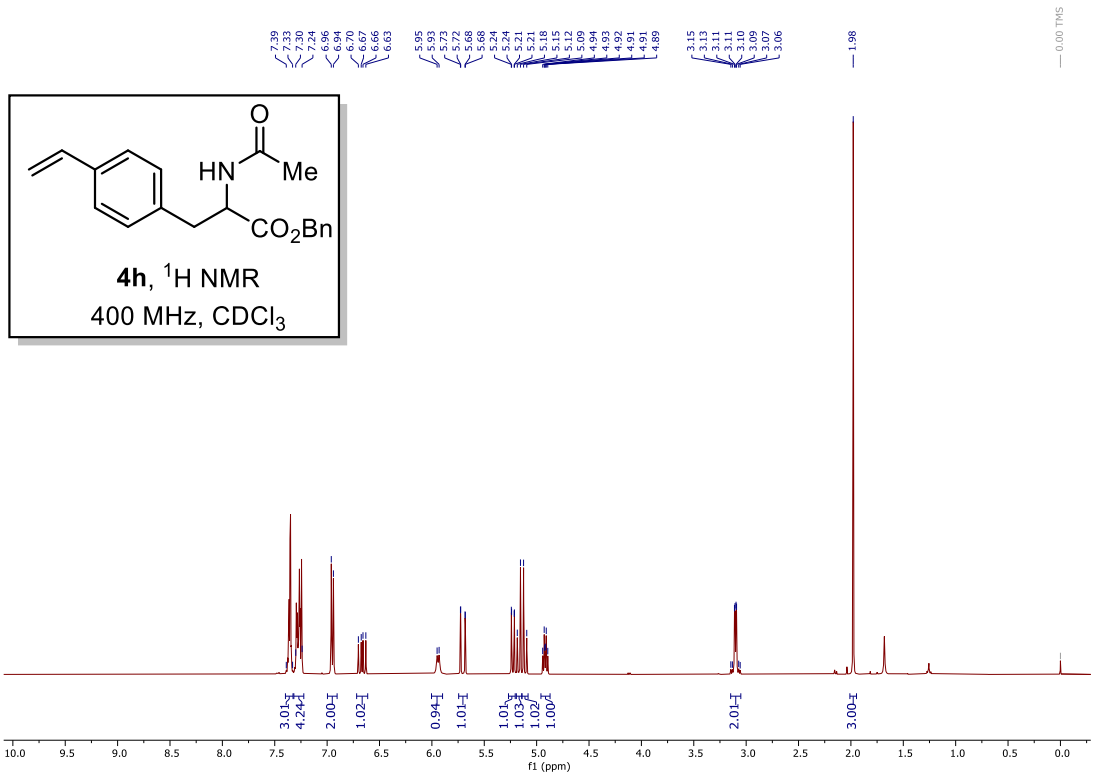
HN
O
Me
CO2Bn
4g, 1H NMR
400 MHz, CDCl3
f1 (ppm)


TBSO
HN
O
Me
CO2Bn
4g, 13C NMR
101 MHz, CDCl3
f1 (ppm)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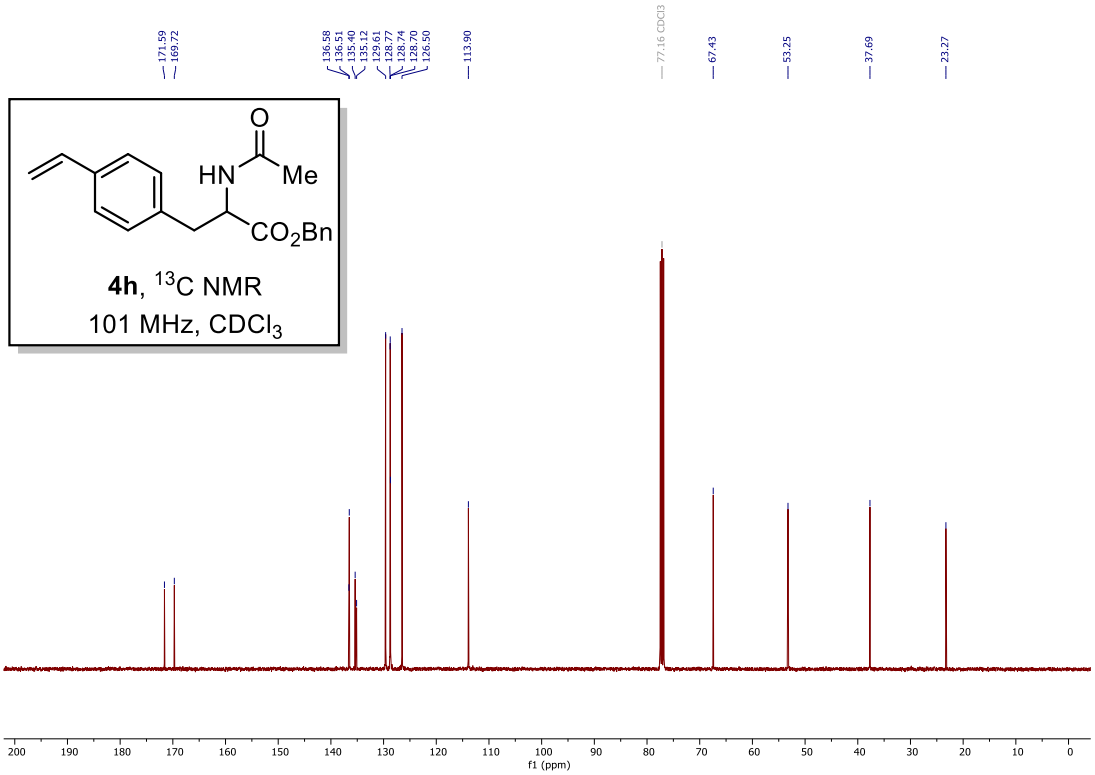
Me
O
CO2Bn
4h, 1H NMR
400 MHz, CDCl3
f1 (ppm)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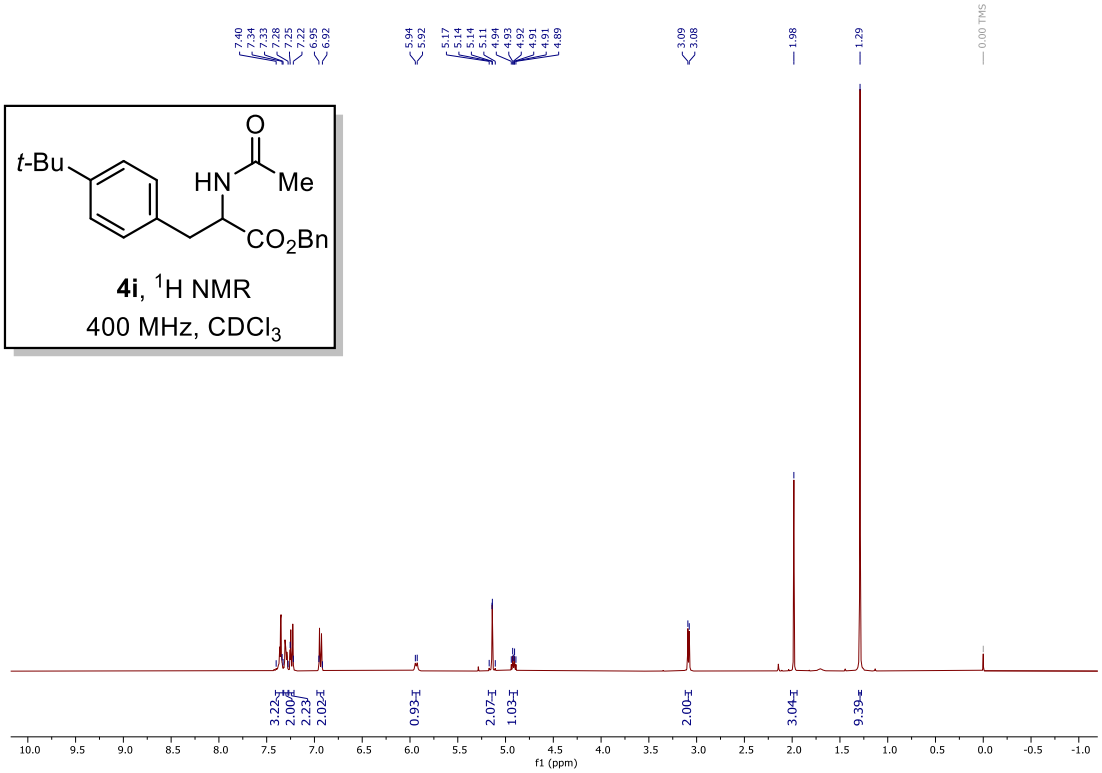
Me
O
CO2Bn
4h, 13C NMR
101 MHz, CDCl3
f1 (ppm)


t-Bu
HN
O
Me
CO2Bn
4i, 1H NMR
400 MHz, CDCl3
7.40
7.34
7.33
7.28
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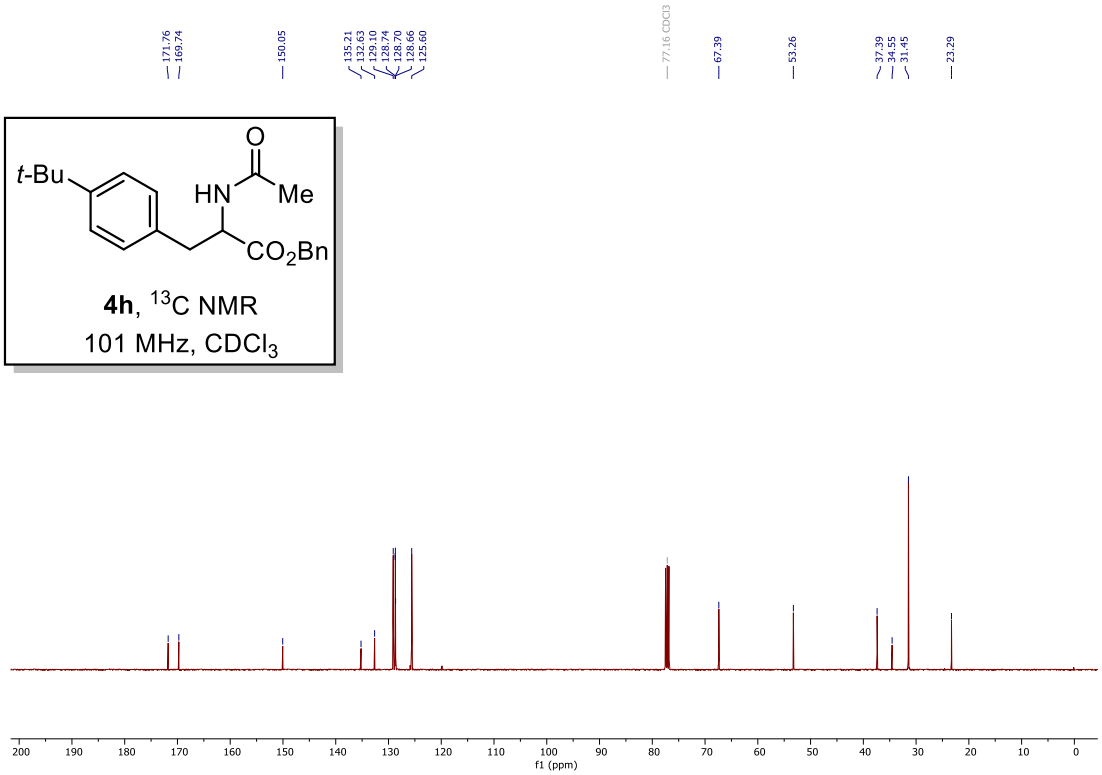
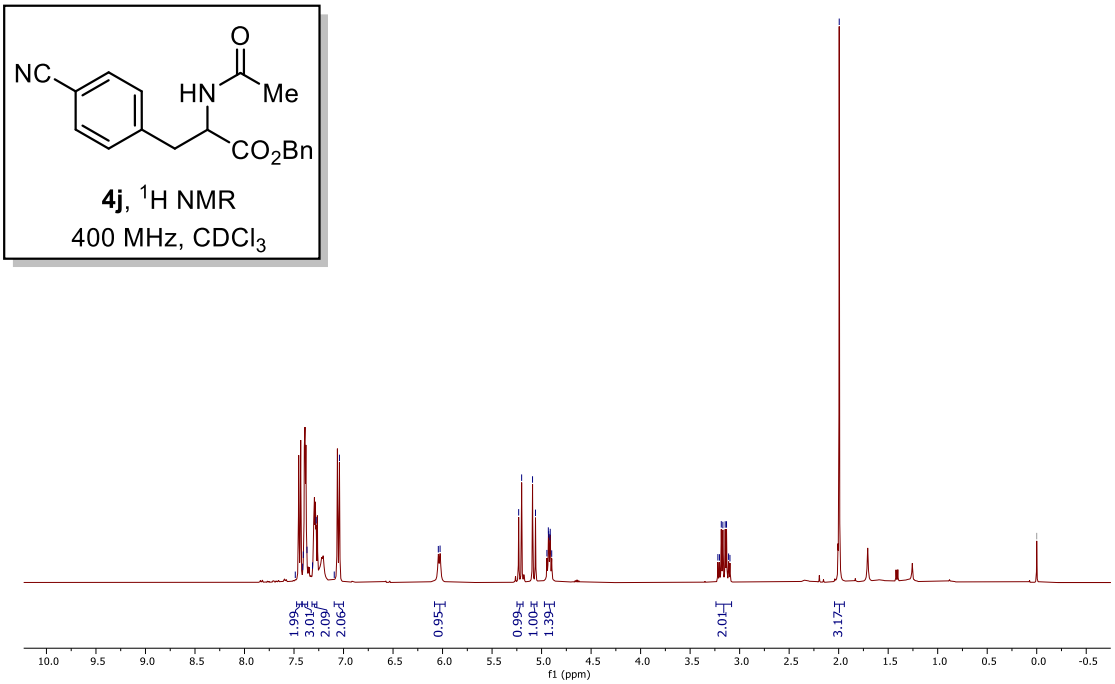
7.22
6.95
6.92
5.94
5.92
5.17
5.14
5.14
5.11
4.94
4.93
4.92
4.91
4.91
4.89
3.09
3.08
1.98
1.29
0.00 TMS
3.22
2.00
2.23
2.02
0.93
2.07
1.03
2.00
3.04
9.39
f1 (ppm)


t-Bu
HN
O
Me
CO2Bn
4h, 13C NMR
101 MHz, CDCl3
171.76
169.74
150.05
135.21
132.63
129.10
128.74
128.70
126.66
125.60
77.16 CDCl3
67.39
53.26
37.39
34.55
31.45
23.29
f1 (ppm)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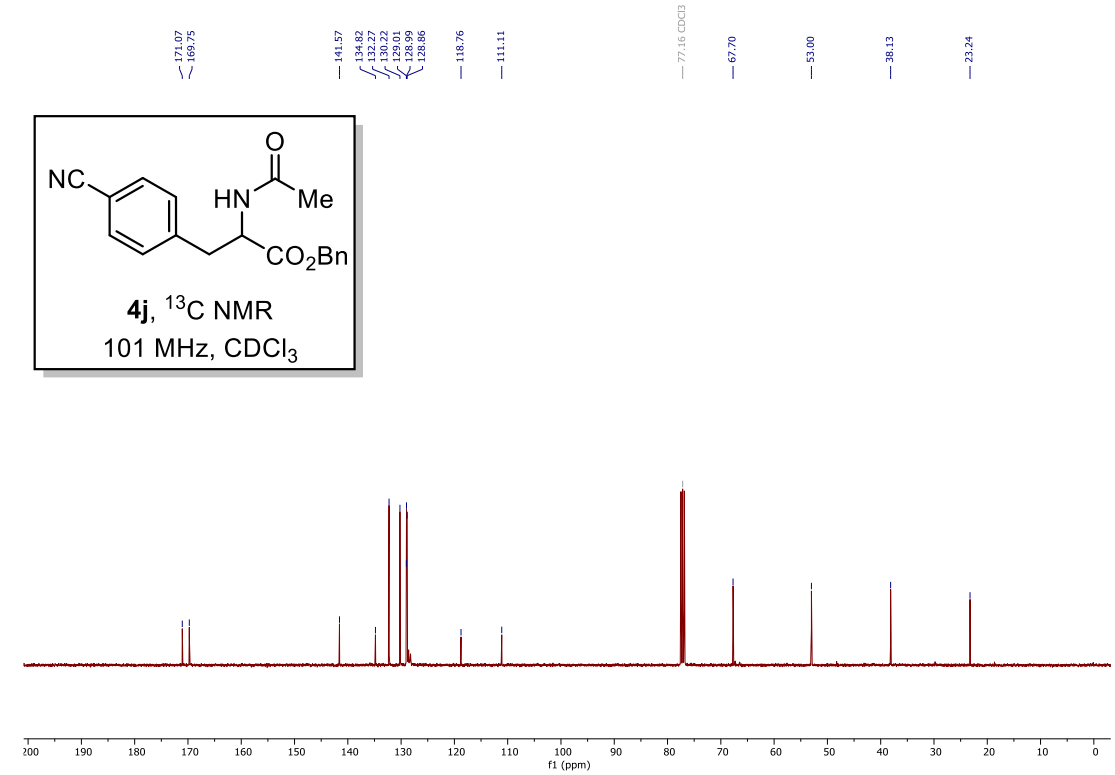
O
Me
CO2Bn
4j, 1H NMR
400 MHz, CDCl3
f1 (ppm)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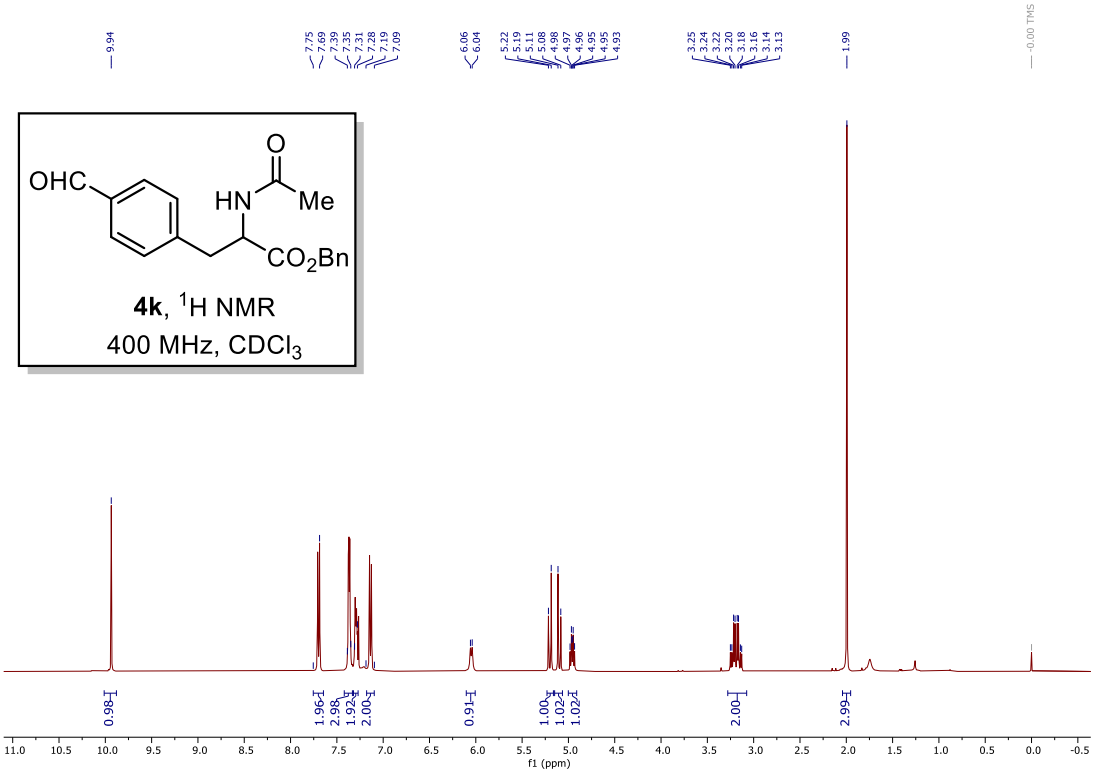
HN
O
Me
CO2Bn
4j, 13C NMR
101 MHz, CDCl3
f1 (ppm)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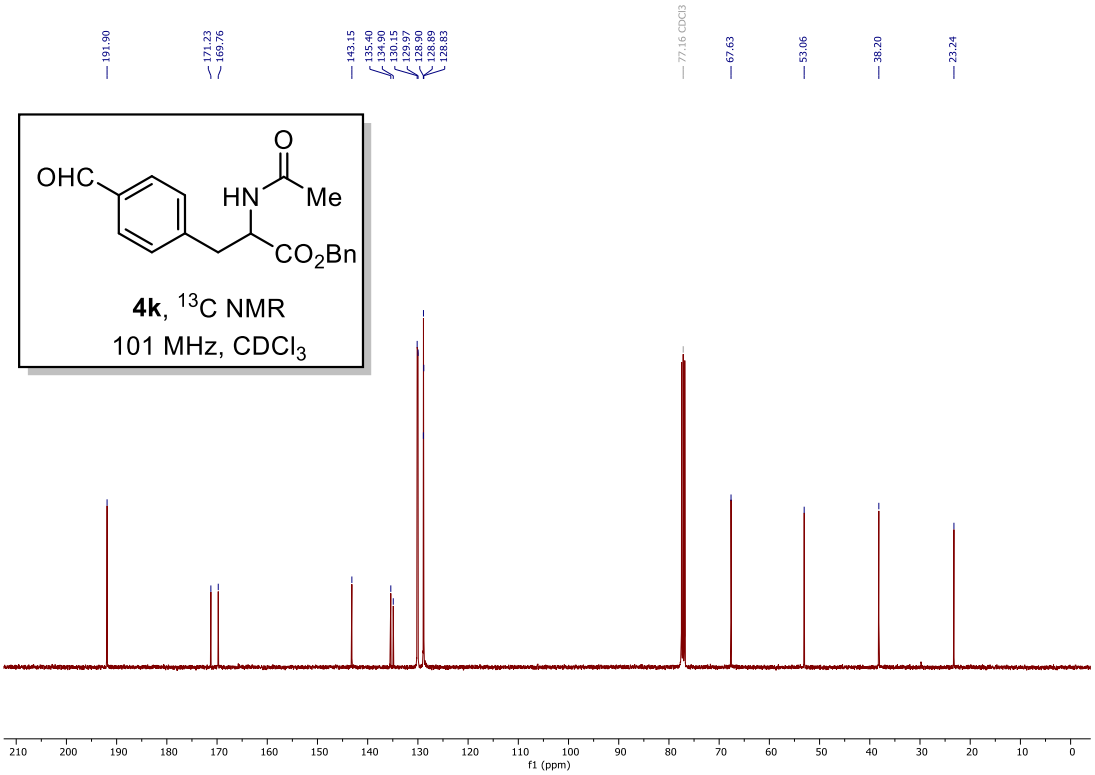
HN
O
Me
CO2Bn
4k, 1H NMR
400 MHz, CDCl3
f1 (ppm)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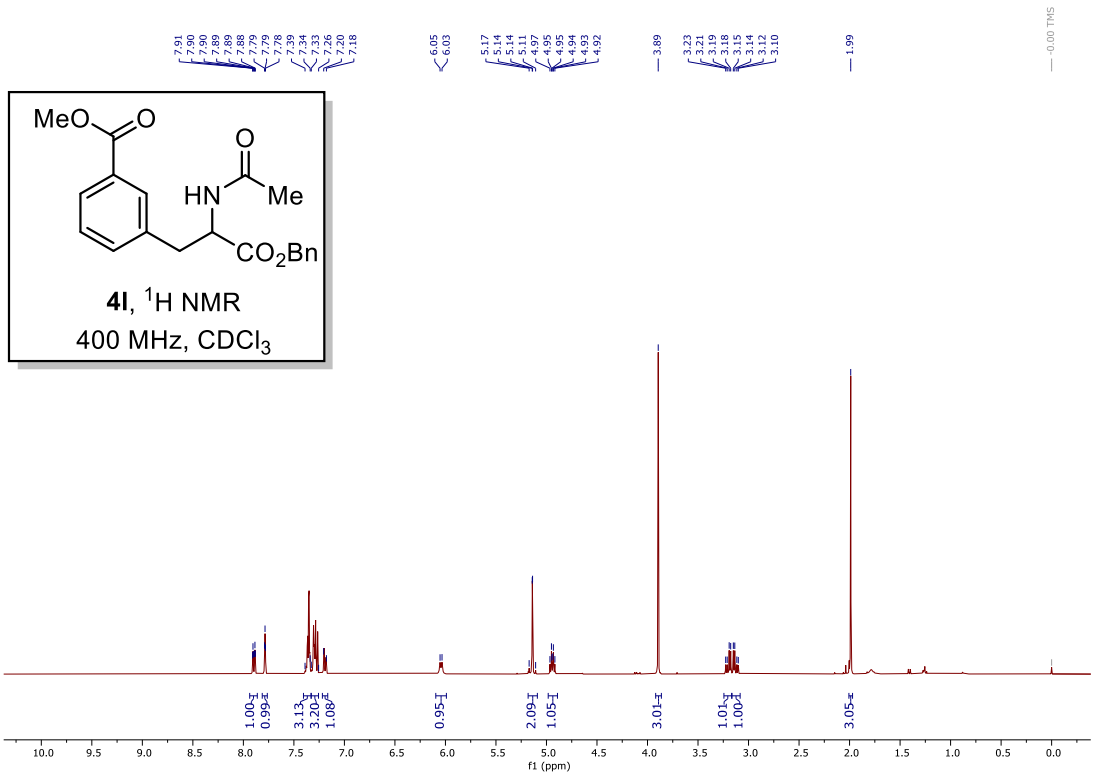
HN
O
Me
CO2Bn
4k, 13C NMR
101 MHz, CDCl3
f1 (ppm)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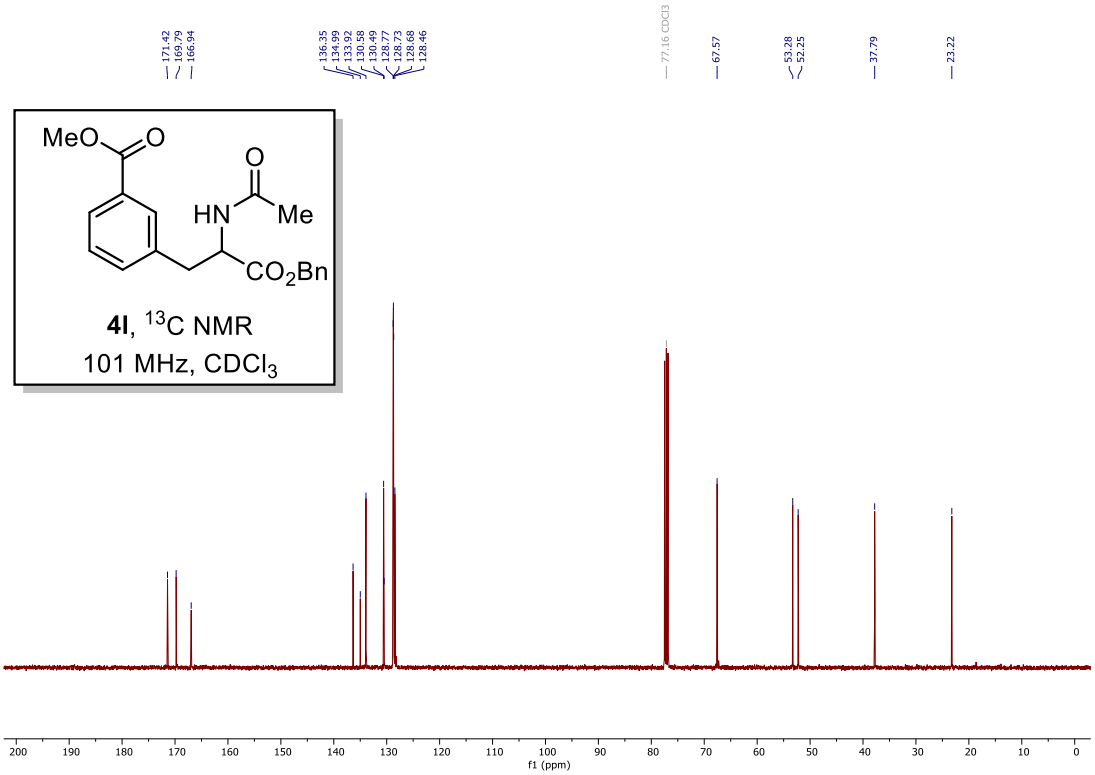
O
HN
O
Me
CO2Bn
4l, 1H NMR
400 MHz, CDCl3
f1 (ppm)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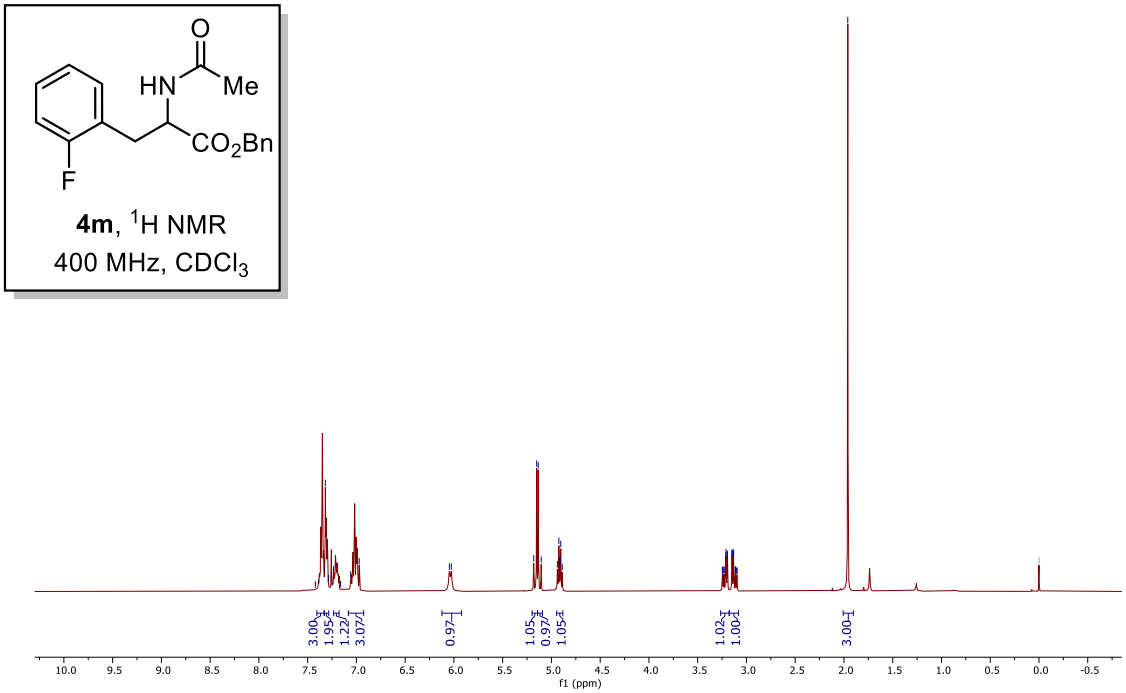
Me
CO2Bn
4l, 13C NMR
101 MHz, CDCl3
f1 (ppm)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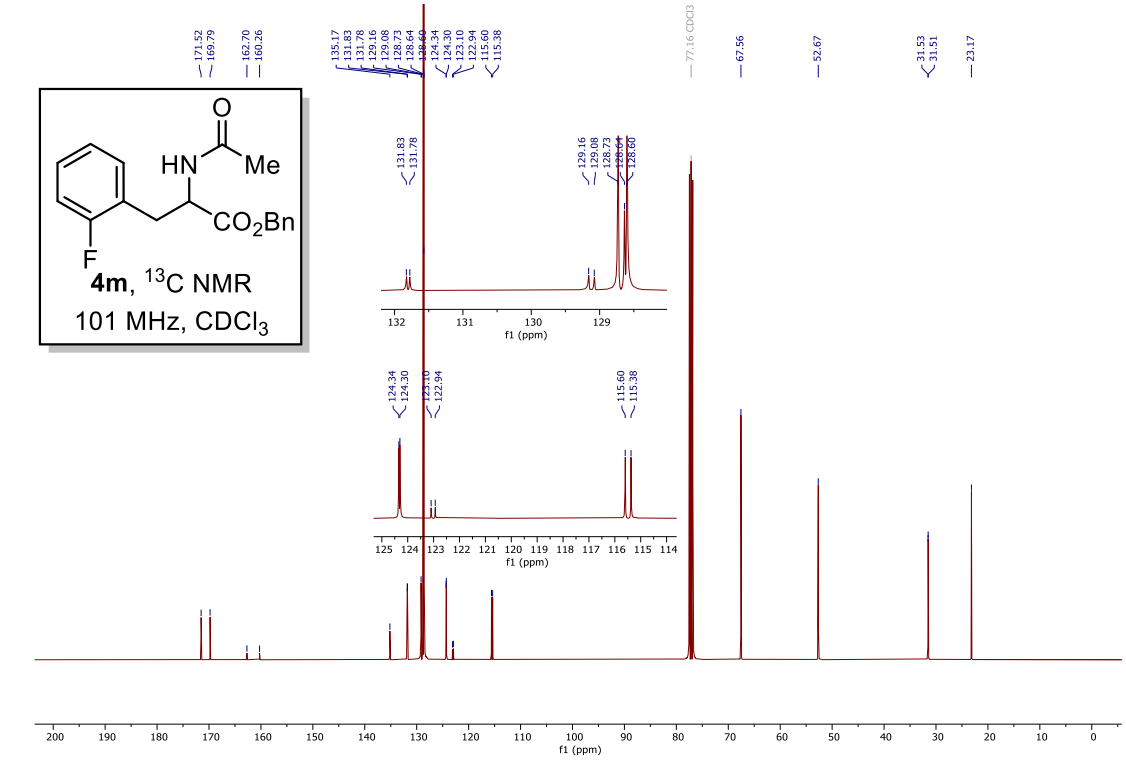
Me
CO2Bn
F
4m, 1H NMR
400 MHz, CDCl3
f1 (ppm)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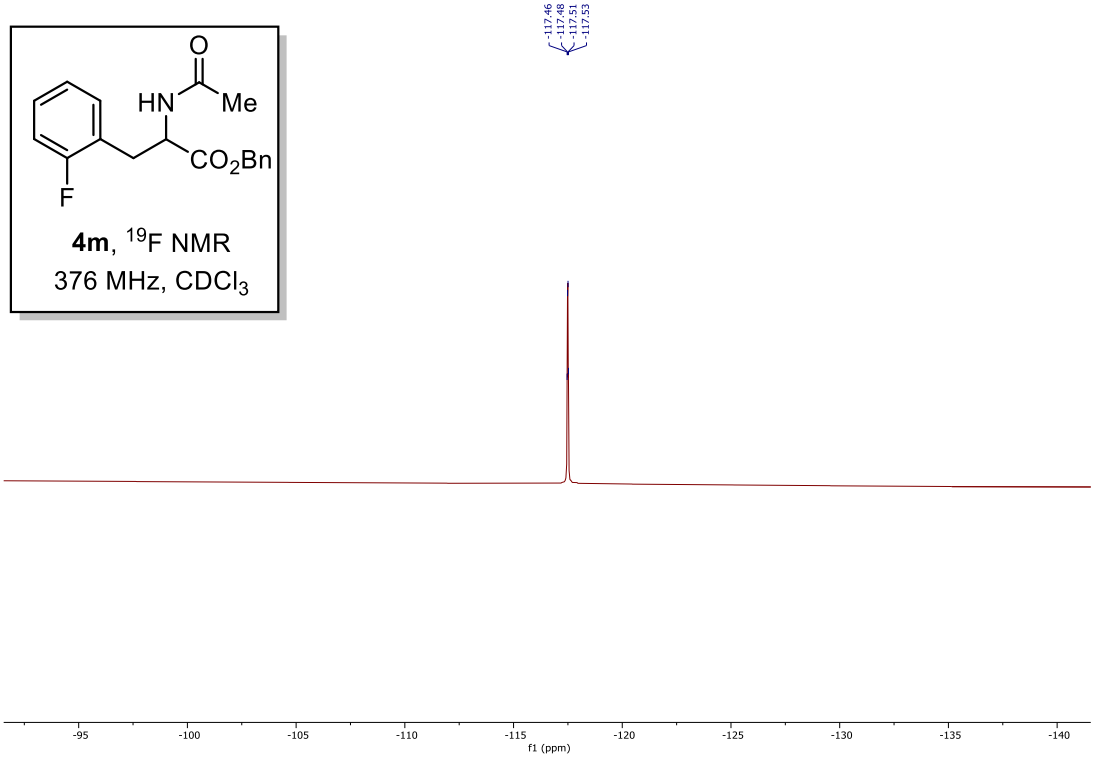
Me
CO2Bn
F
4m, 13C NMR
101 MHz, CDCl3
f1 (ppm)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-117.48
-117.51
-117.53
O
HN
Me
CO2Bn
F
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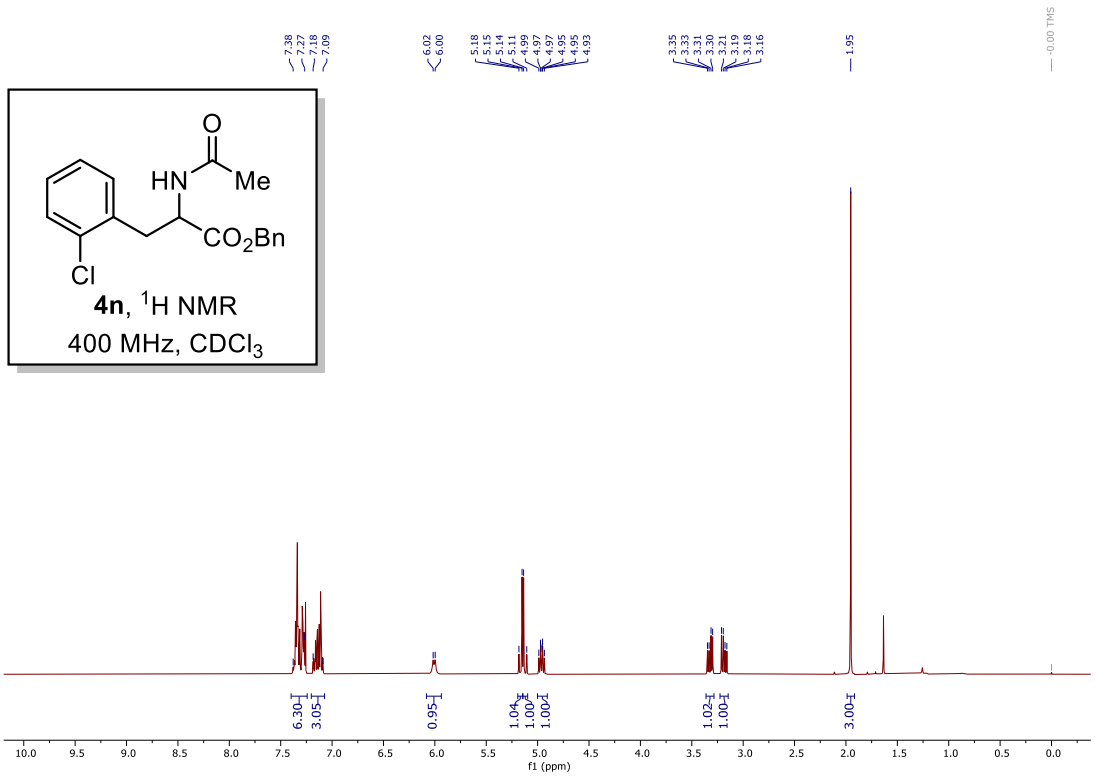
-135
-140
f1 (ppm)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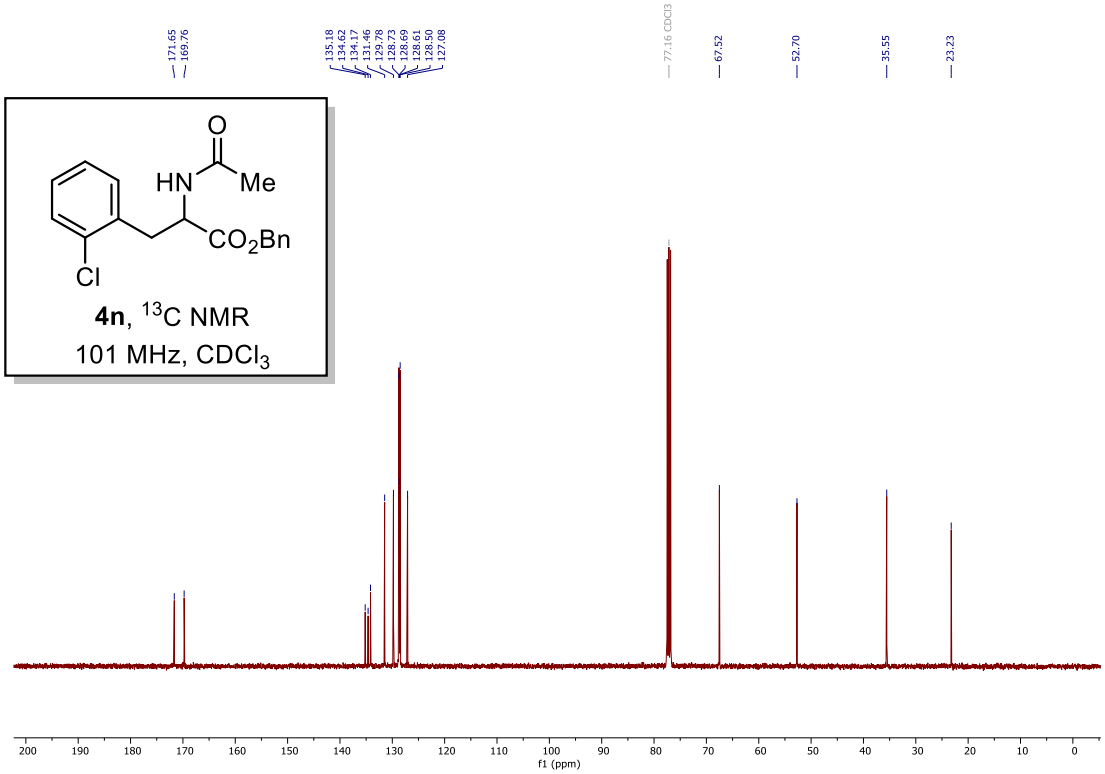
Me
CO2Bn
Cl
4n, 1H NMR
400 MHz, CDCl3
f1 (ppm)


O
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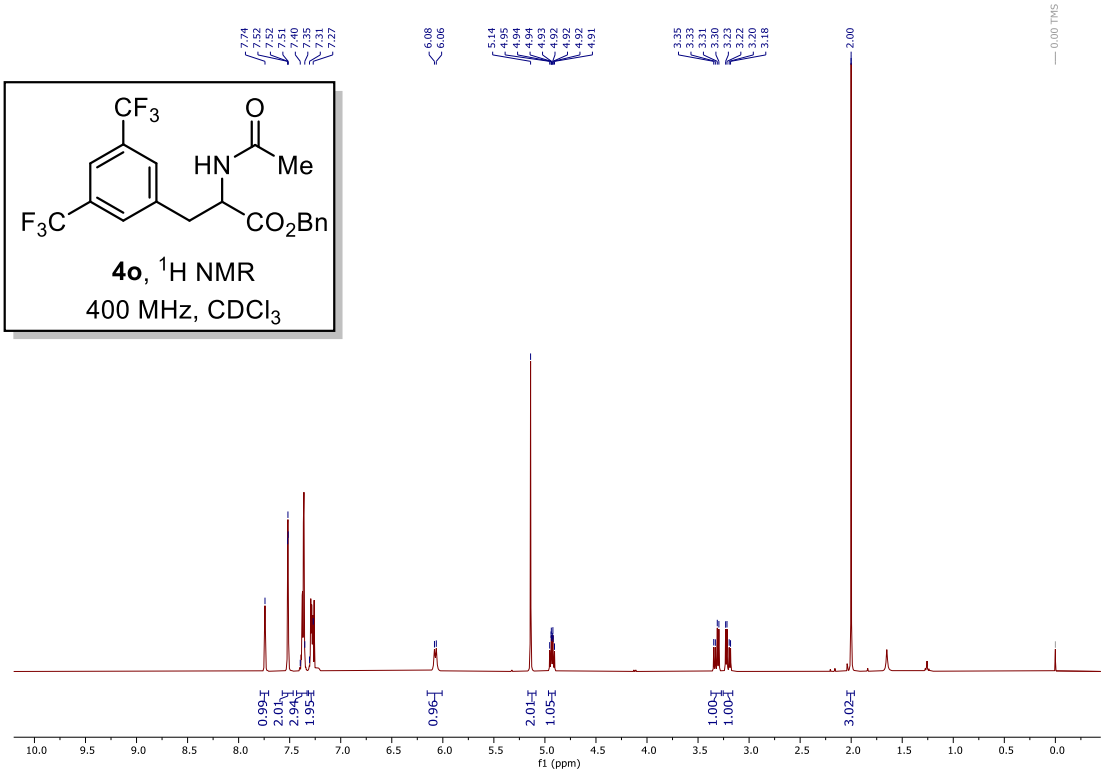
Me
CO2Bn
Cl
4n, 13C NMR
101 MHz, CDCl3
f1 (ppm)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O
HN
Me
F3C
CO2Bn
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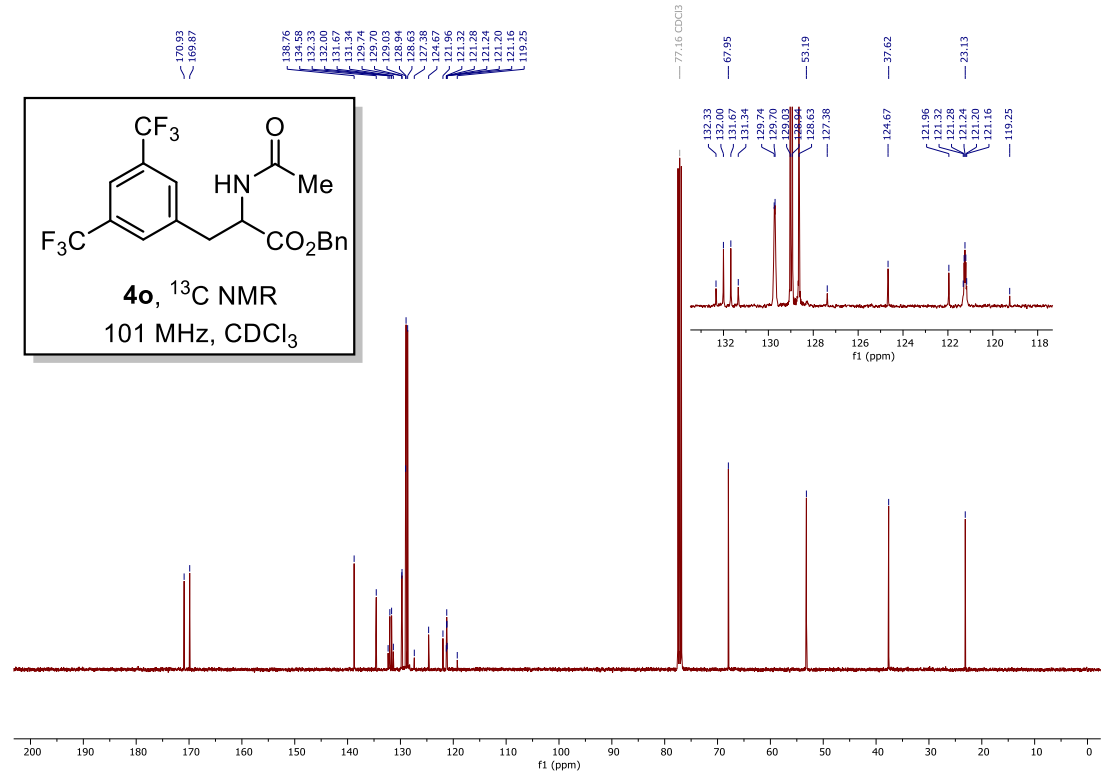
400 MHz, CDCl3
f1 (ppm)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HN
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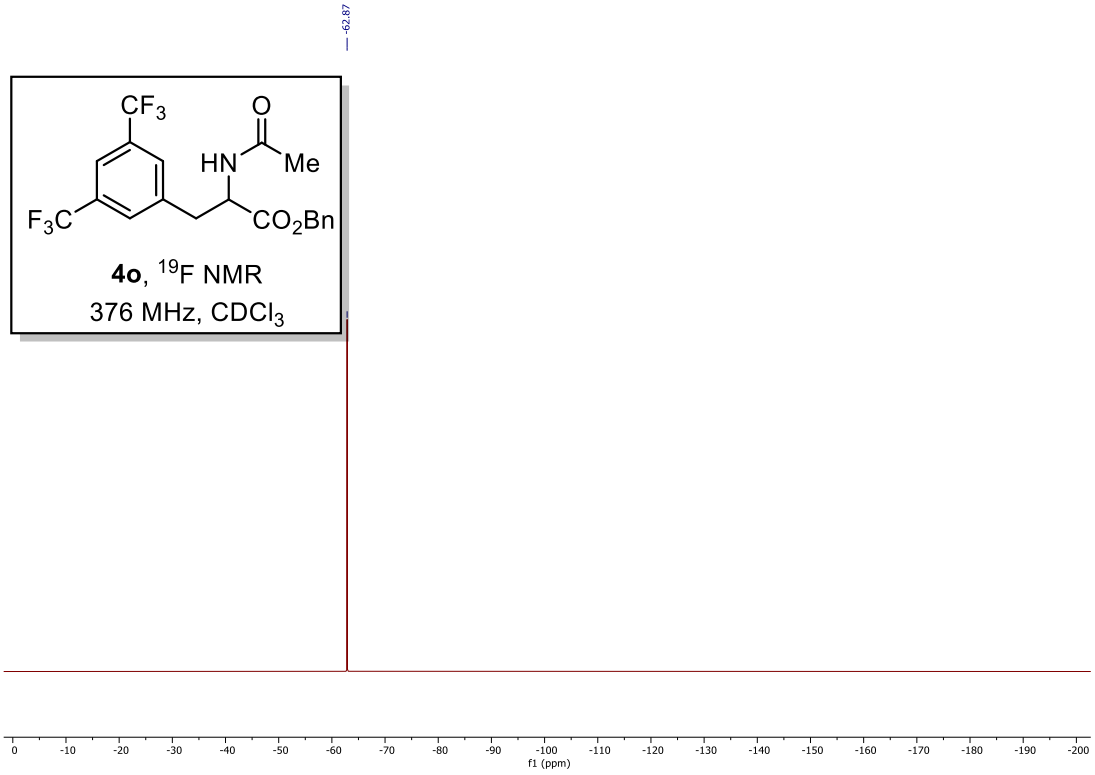
F3C
CO2Bn
4o, 13C NMR
101 MHz, CDCl3
f1 (ppm)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HN
Me
F3C
CO2Bn
4o, 19F NMR
376 MHz, CDCl3
0
-10
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-30
-40
-50
-60
-70
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-90
-100
-110
-120
-130
-140
-150
-160
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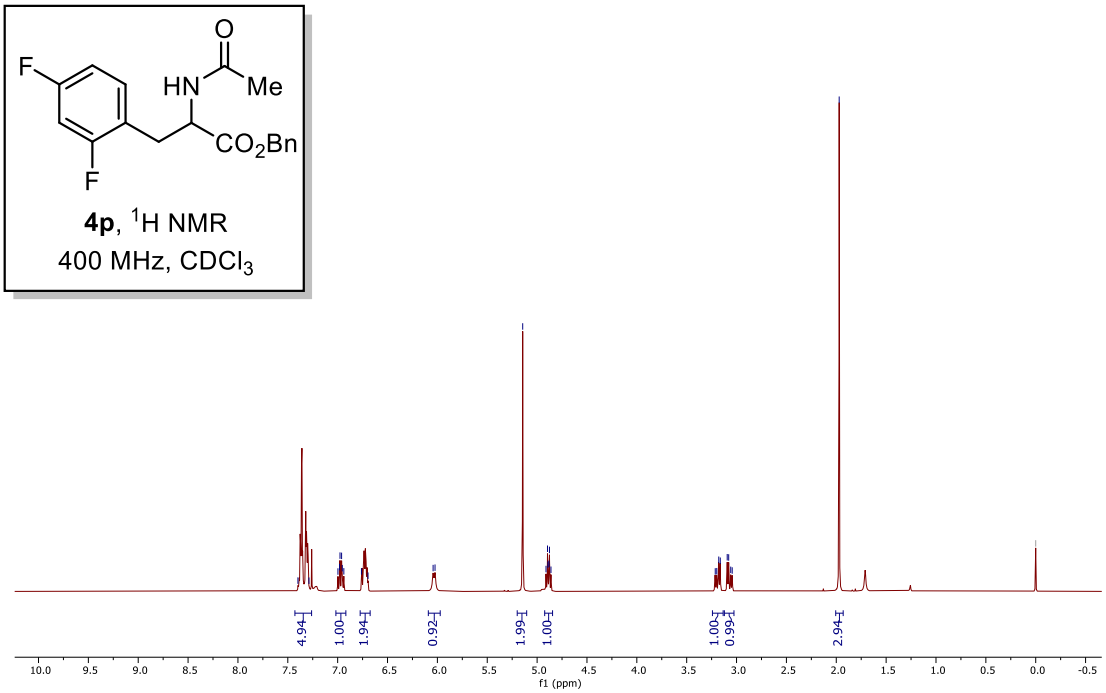
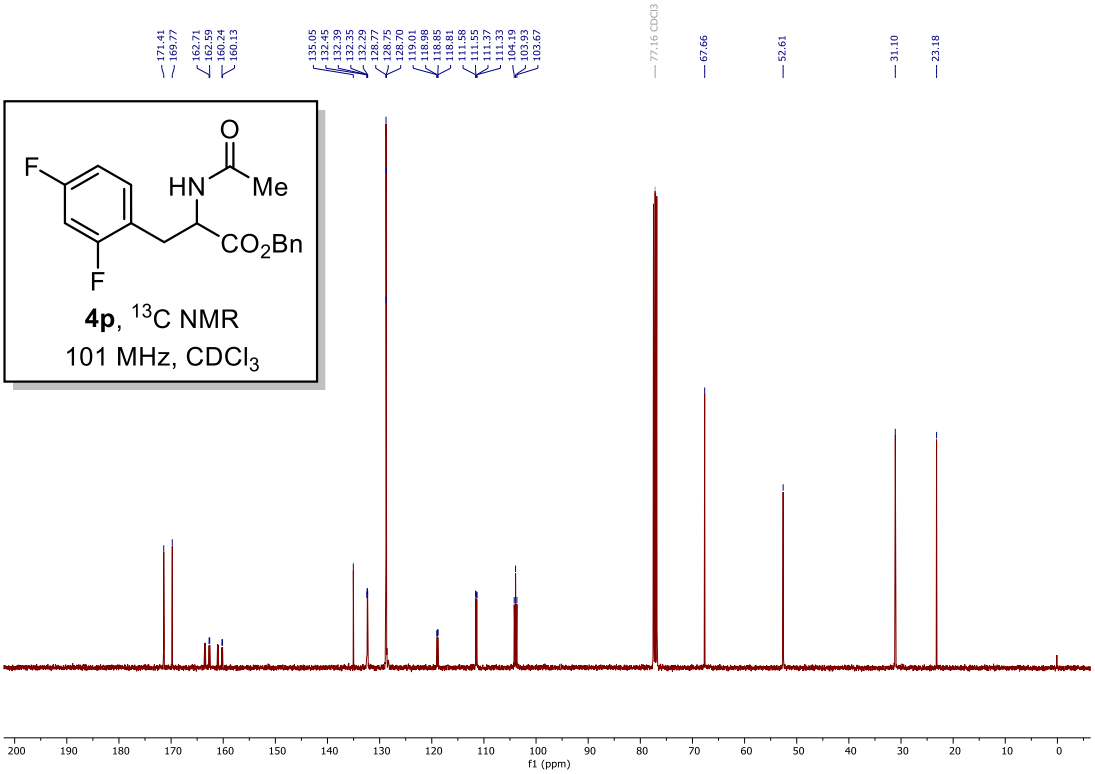
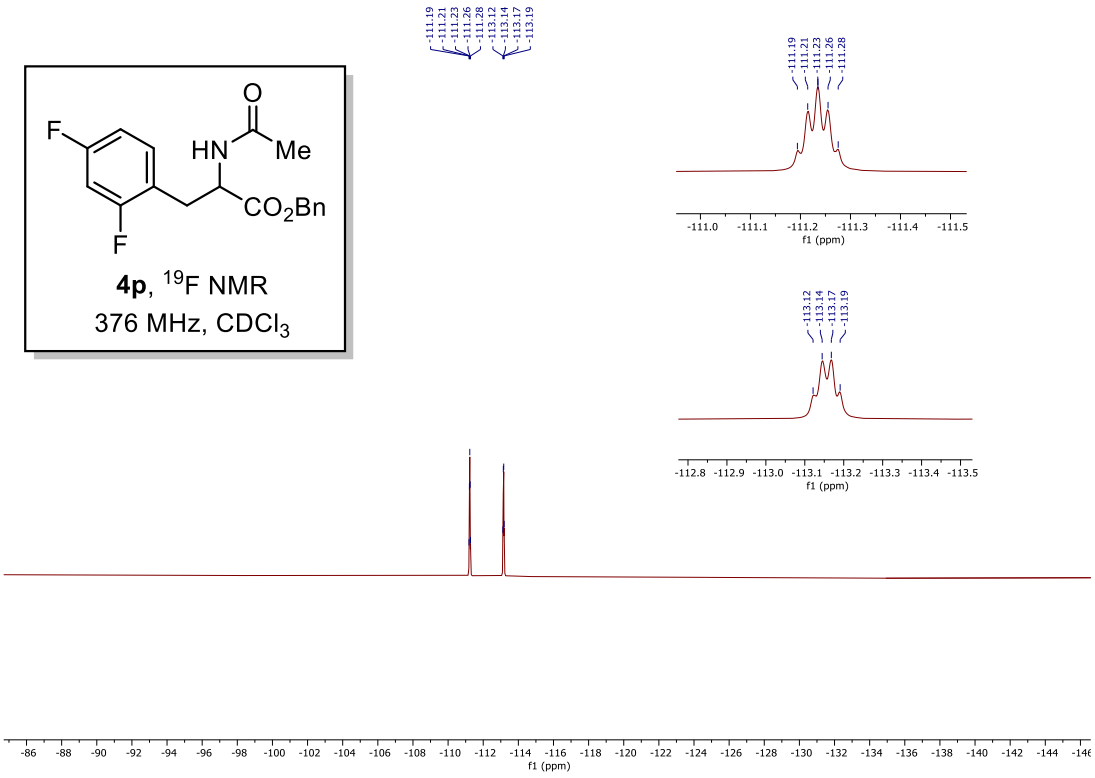
-190
-200
f1 (ppm)


F
O
HN
Me
CO2Bn
F
4p, 1H NMR
400 MHz, CDCl3
f1 (ppm)


F
O
HN
Me
CO2Bn
F
4p, 13C NMR
101 MHz, CDCl3
f1 (ppm)


F
O
HN
Me
CO2Bn
F
4p, 19F NMR
376 MHz, CDCl3
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-111.21
-111.23
-111.26
-111.28
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-113.14
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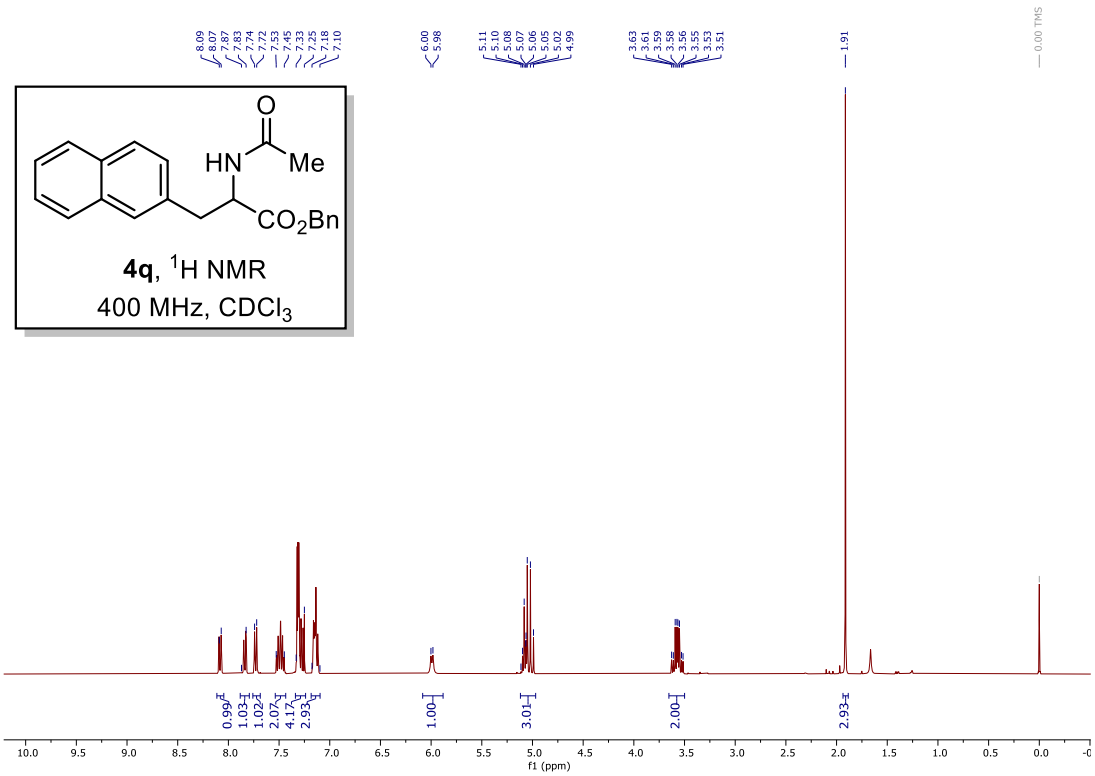
-113.19
f1 (ppm)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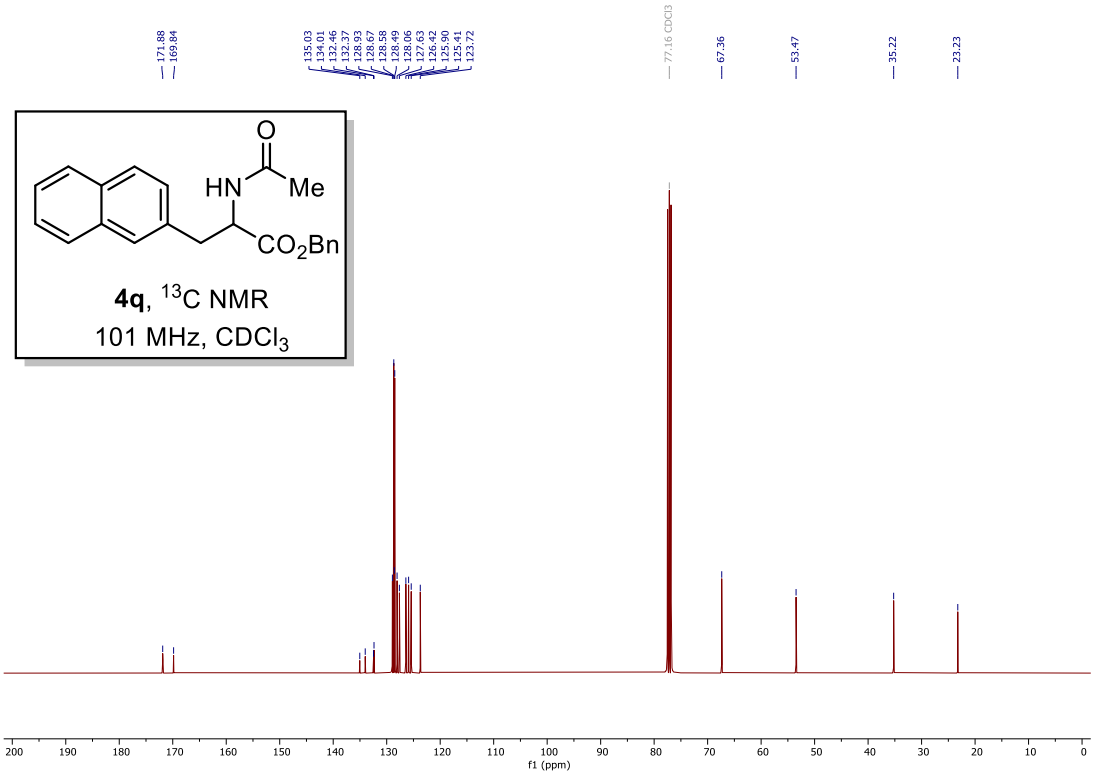
Me
CO2Bn
4q, 1H NMR
400 MHz, CDCl3
f1 (ppm)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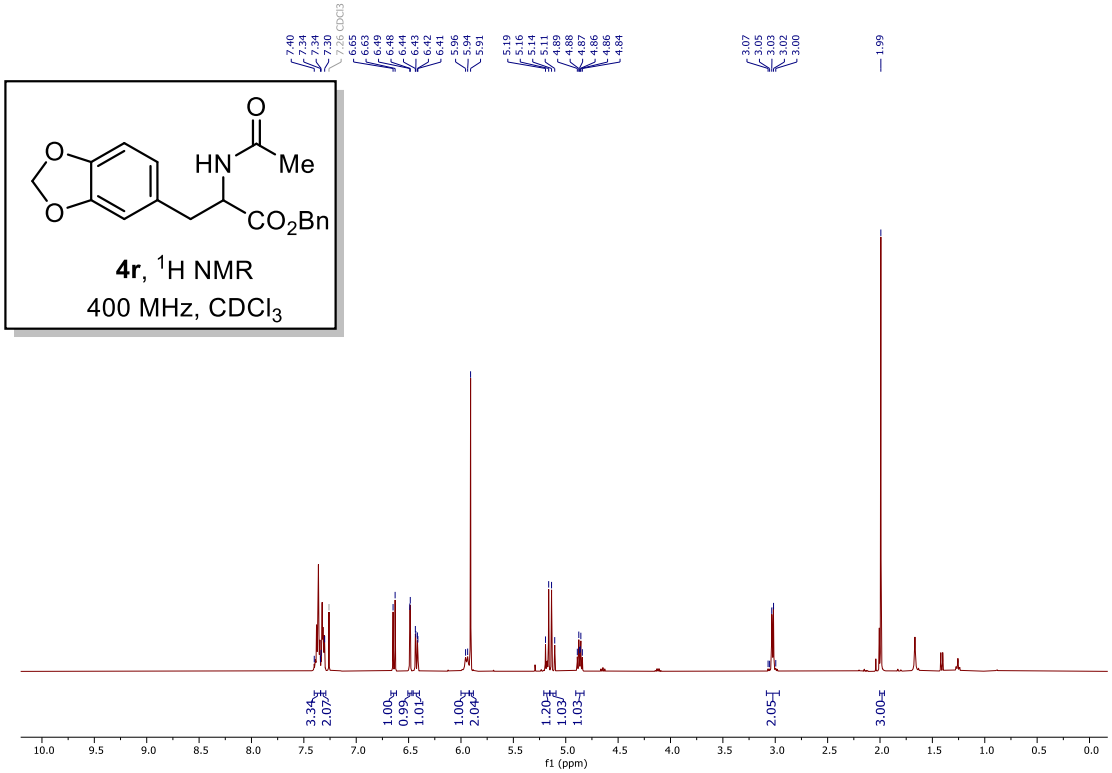
O
Me
CO2Bn
4q, 13C NMR
101 MHz, CDCl3
f1 (ppm)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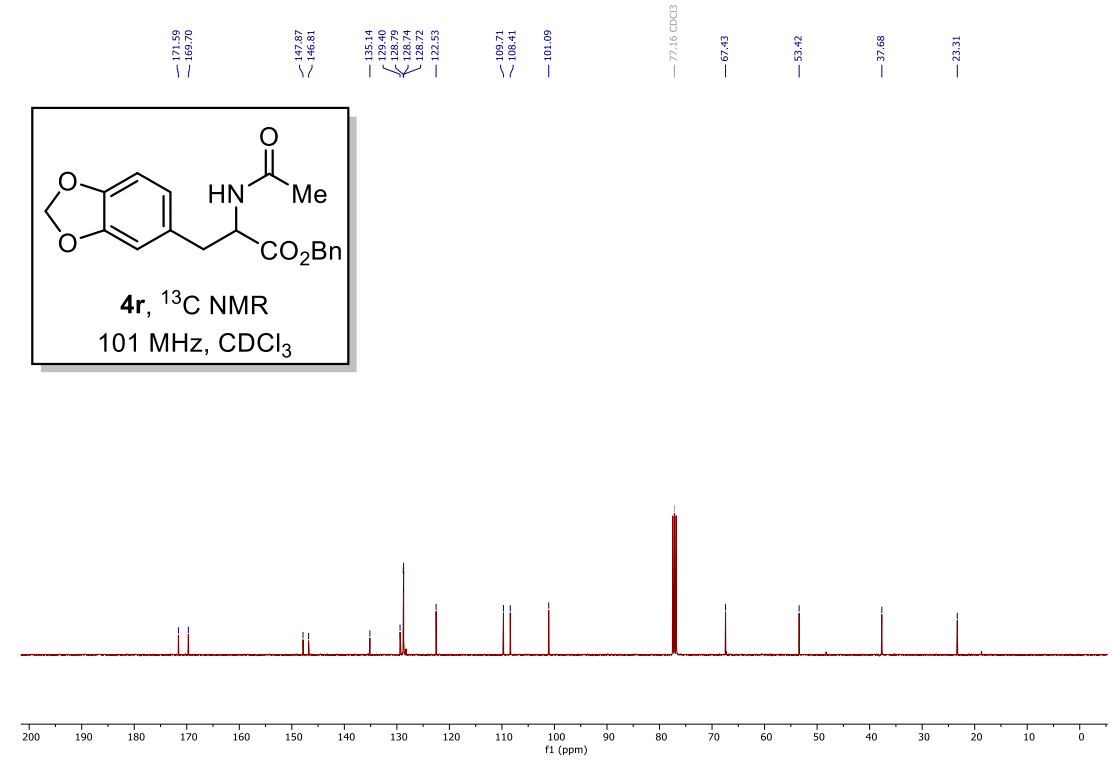
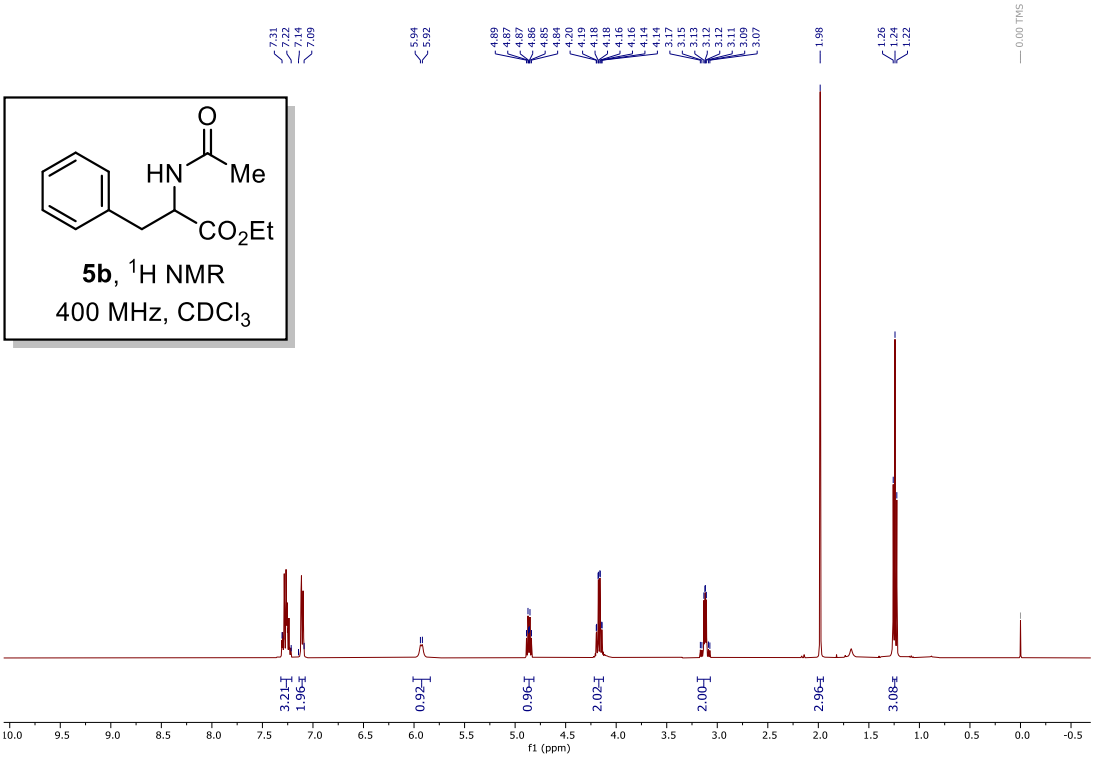
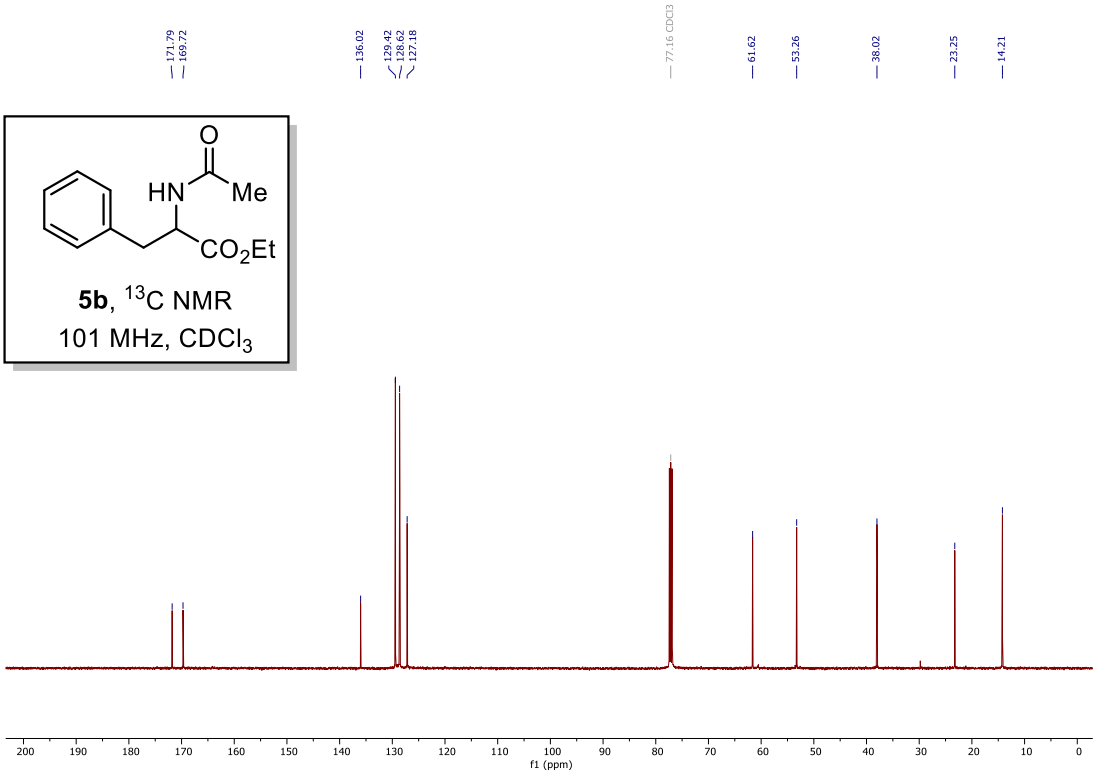
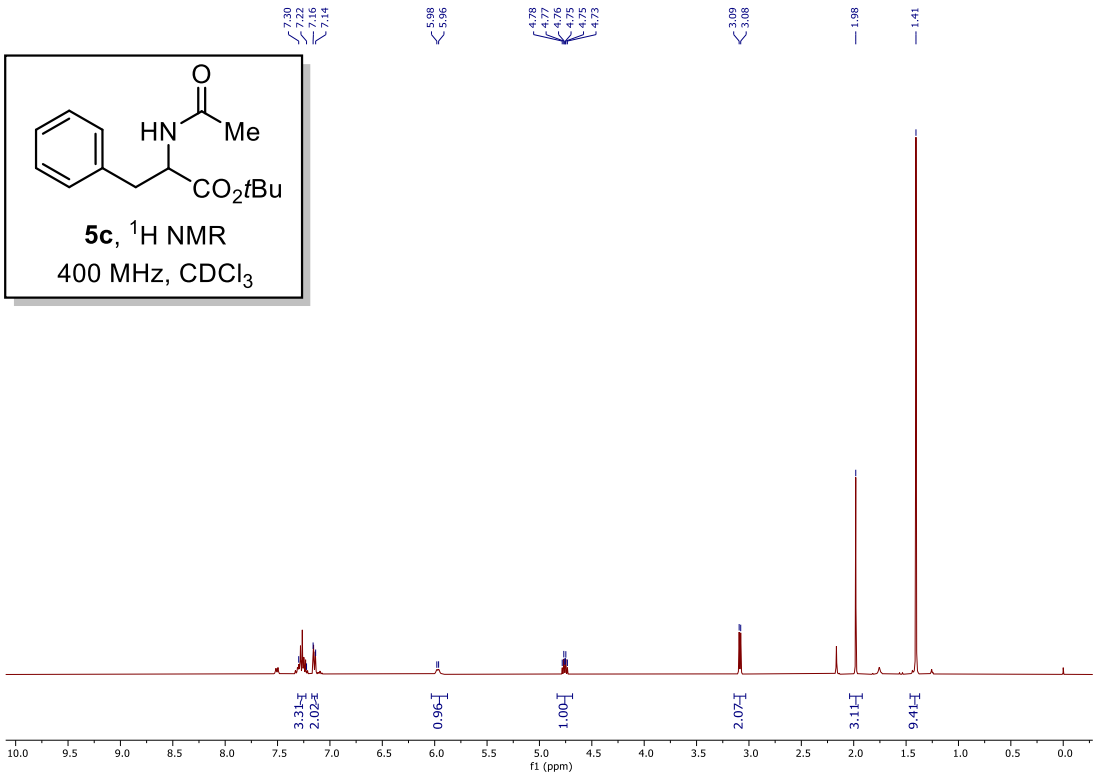
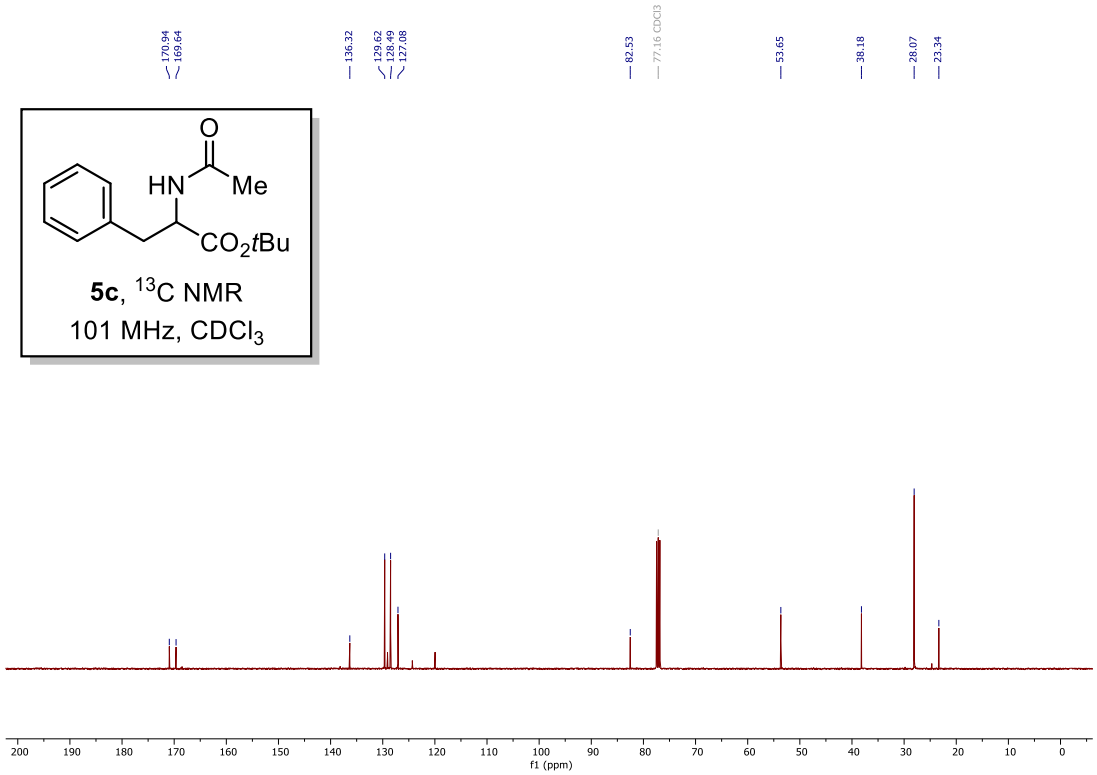
CO2Bn
4r, 1H NMR
400 MHz, CDCl3
f1 (ppm)

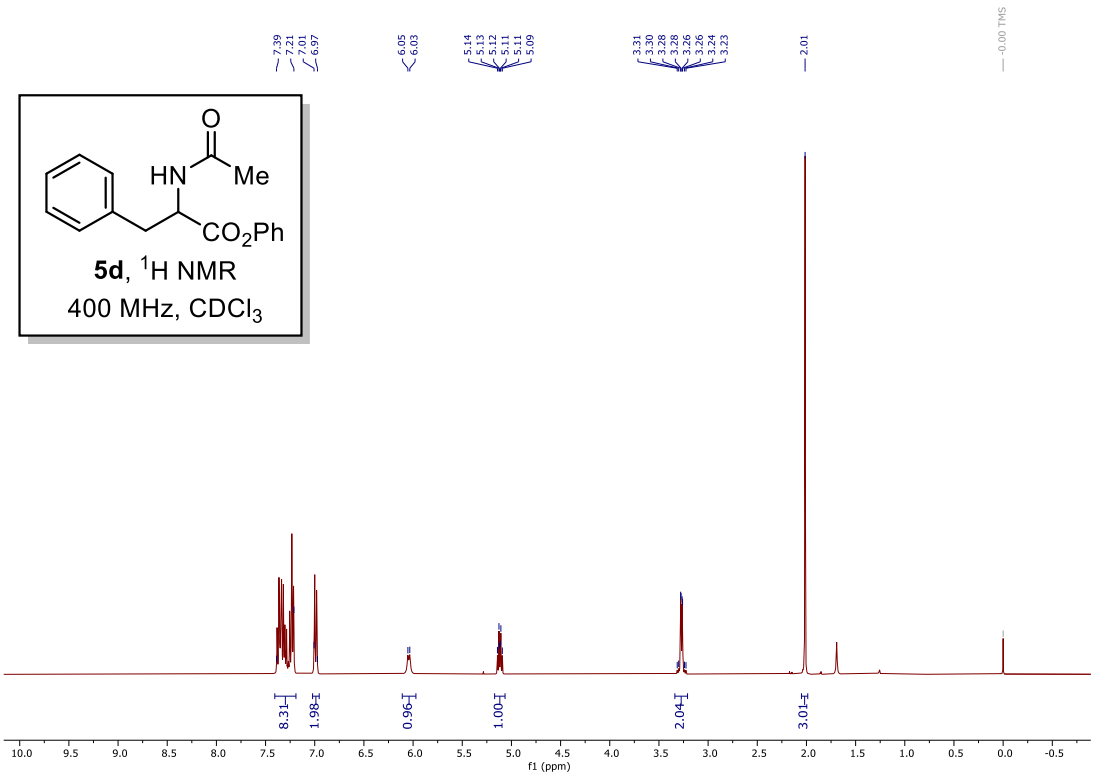

HN
Me
CO2Bn
4r, 13C NMR
101 MHz, CDCl3
f1 (ppm)


O
HN
Me
CO2Et
5b, 1H NMR
400 MHz, CDCl3
7.31
7.22
7.14
7.09
5.94
5.92
4.89
4.87
4.87
4.86
4.85
4.84
4.20
4.19
4.18
4.18
4.16
4.16
4.14
4.14
3.17
3.15
3.13
3.12
3.12
3.11
3.09
3.07
1.98
1.26
1.24
1.22
0.00 TMS
3.21
1.96
0.92
0.96
2.02
2.00
2.96
3.08
f1 (ppm)

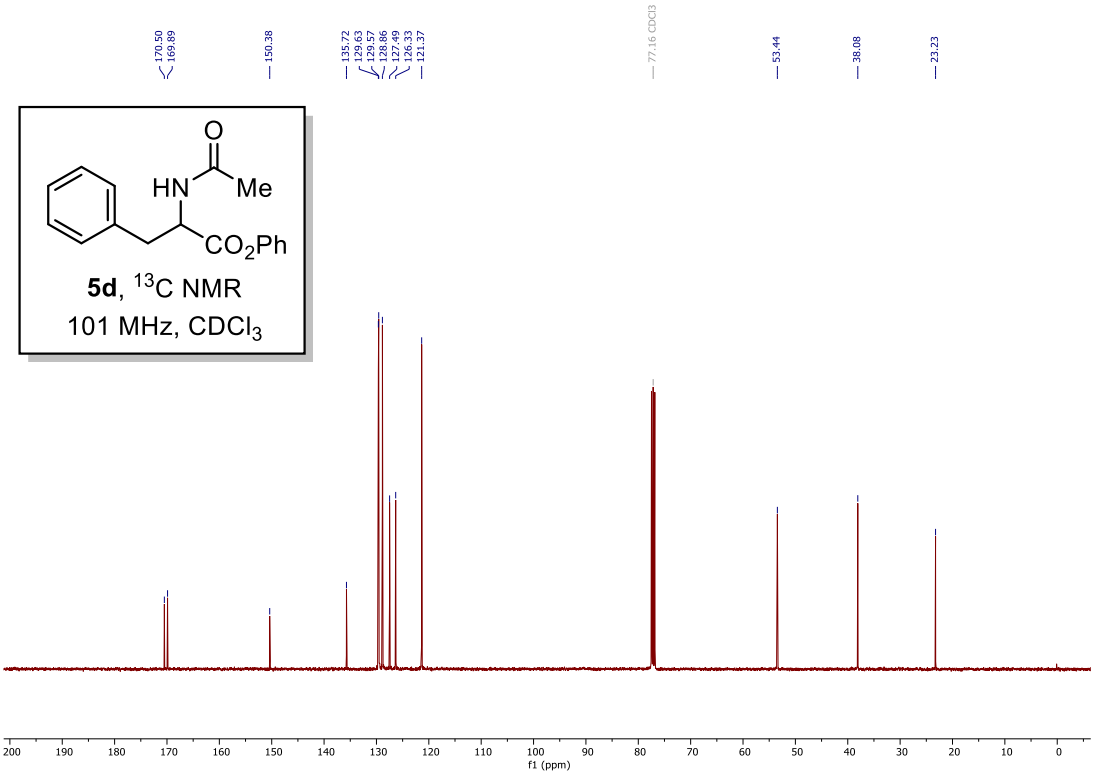

O
HN
Me
CO2Et
5b, 13C NMR
101 MHz, CDCl3
171.79
169.72
136.02
129.42
128.62
127.18
77.16 CDCl3
61.62
53.26
38.02
23.25
14.21
f1 (ppm)


7.30
7.22
7.16
7.14
5.98
5.96
4.78
4.77
4.76
4.75
4.73
3.09
3.08
1.98
1.41
O
HN
Me
CO2tBu
5c, 1H NMR
400 MHz, CDCl3
3.31
2.02
0.96
1.00
2.07
3.11
9.41
f1 (ppm)

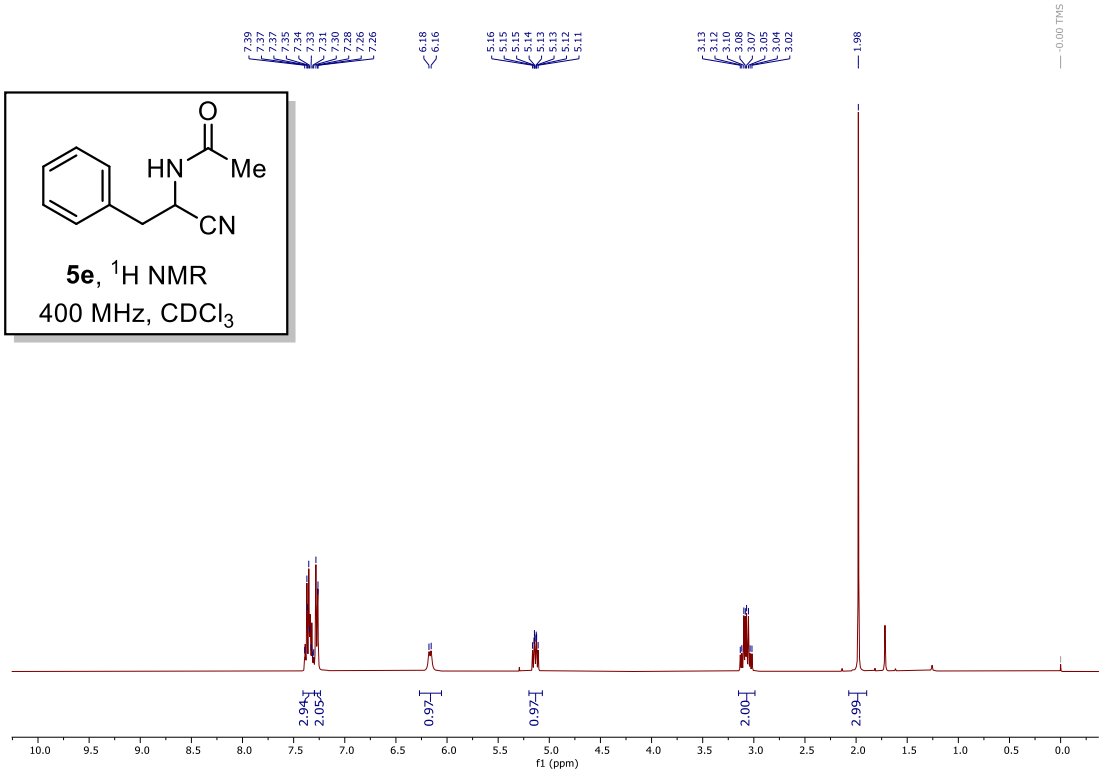

170.94
169.64
136.32
129.62
128.49
127.08
82.53
77.16 CDCl3
53.65
38.18
28.07
23.34
O
HN
Me
CO2tBu
5c, 13C NMR
101 MHz, CDCl3
f1 (ppm)

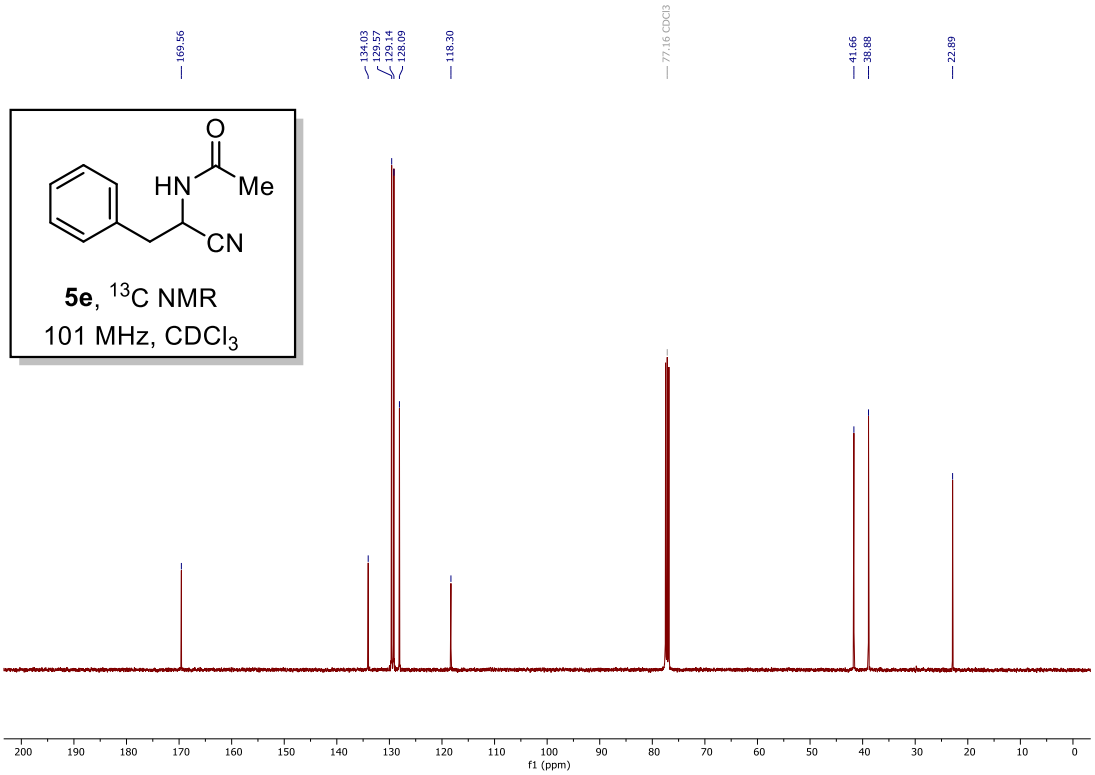


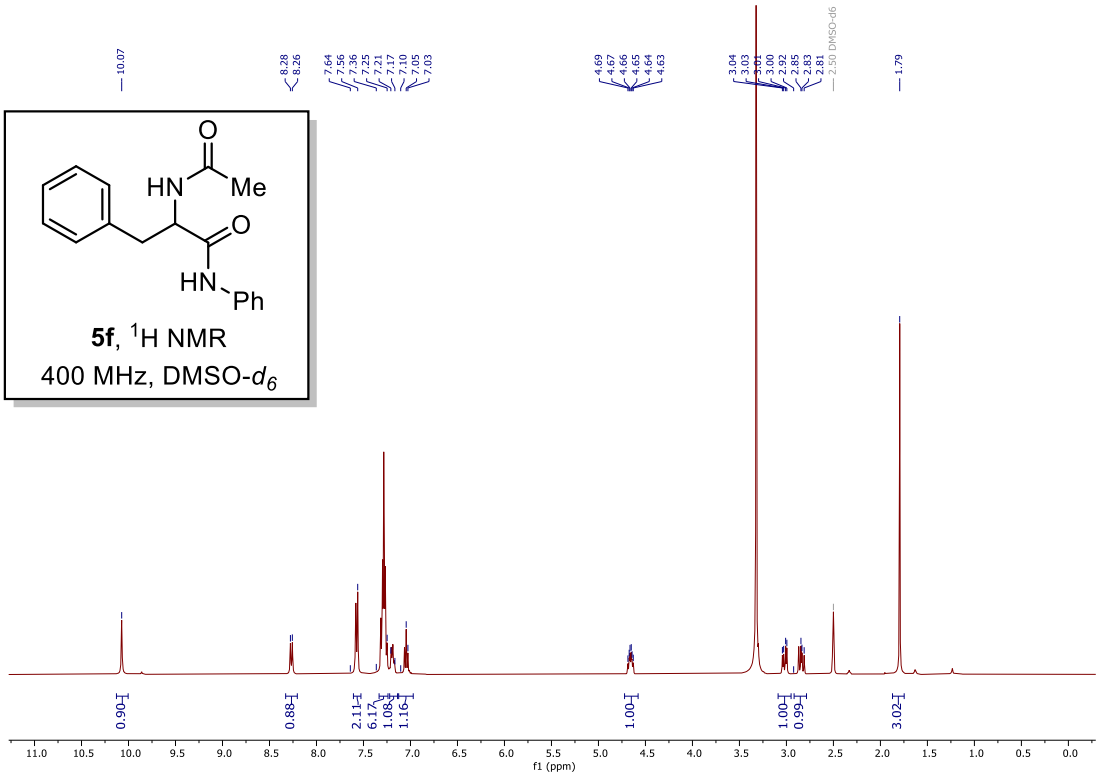
5d, ^{1}H NMR
400 MHz, $CDCl_3$

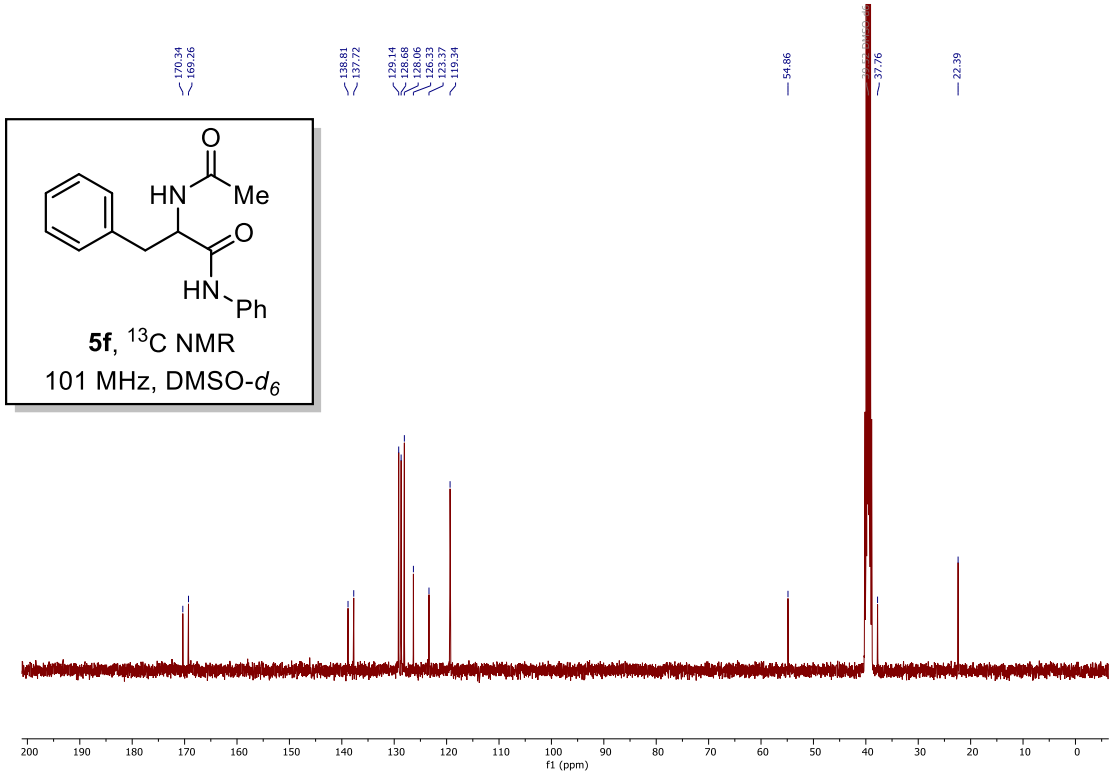


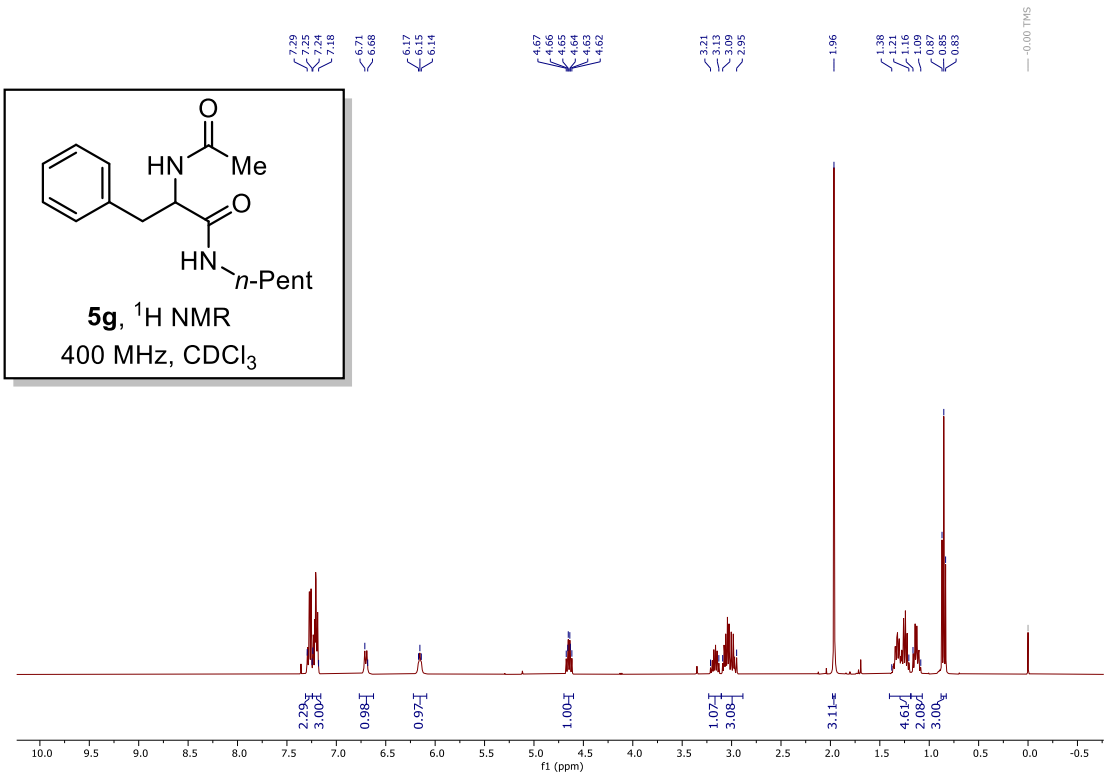
5d, ^{13}C NMR
101 MHz, $CDCl_3$

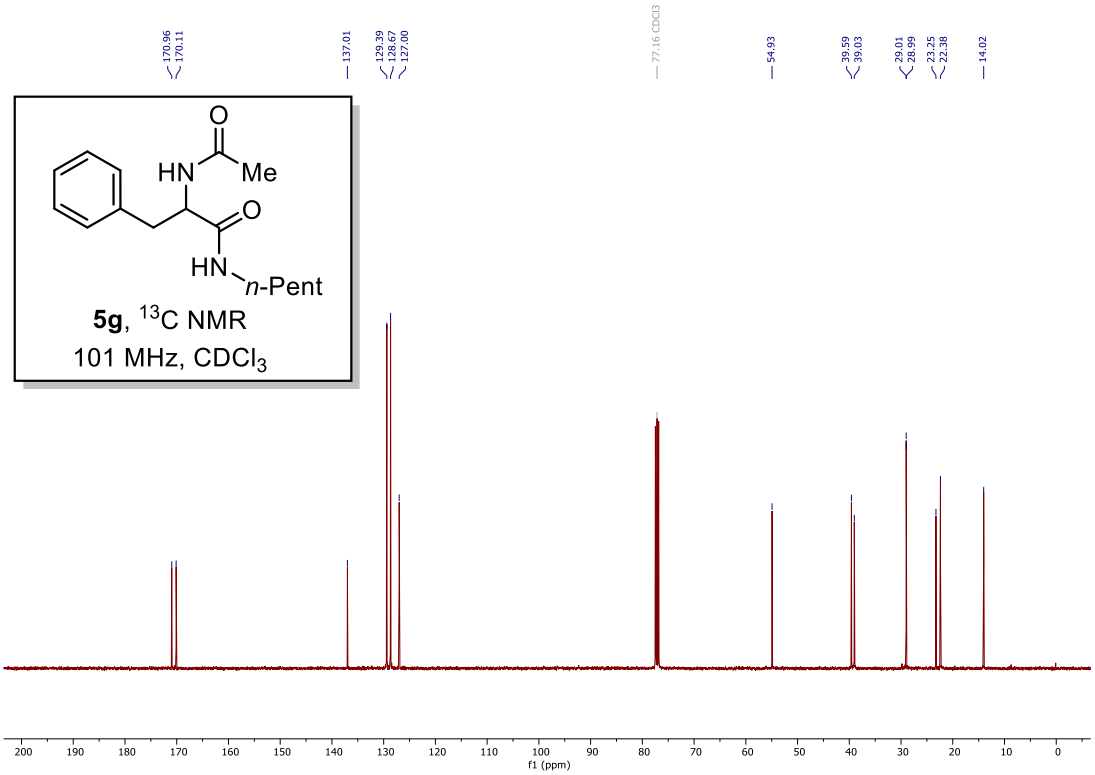

7.39
7.37
7.37
7.35
7.35
7.34
7.33
7.31
7.30
7.28
7.26
7.26
6.18
6.16
5.16
5.15
5.15
5.14
5.13
5.13
5.12
5.11
3.13
3.12
3.10
3.08
3.07
3.05
3.04
3.02
1.98
0.00 TMS
O
HN
Me
CN
5e, 1H NMR
400 MHz, CDCl3
2.94
2.05
0.97
0.97
2.00
2.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

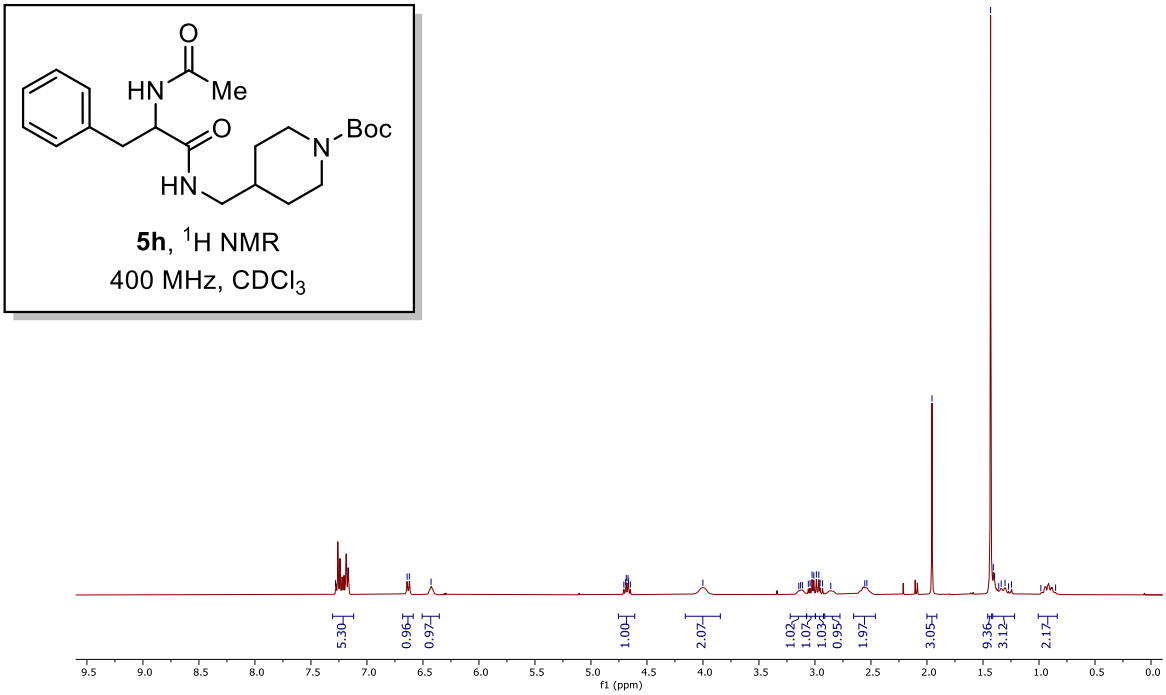

169.56
134.03
129.57
129.14
128.09
118.30
77.16 CDCl3
41.66
38.88
22.89
O
HN
Me
CN
5e, 13C NMR
101 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

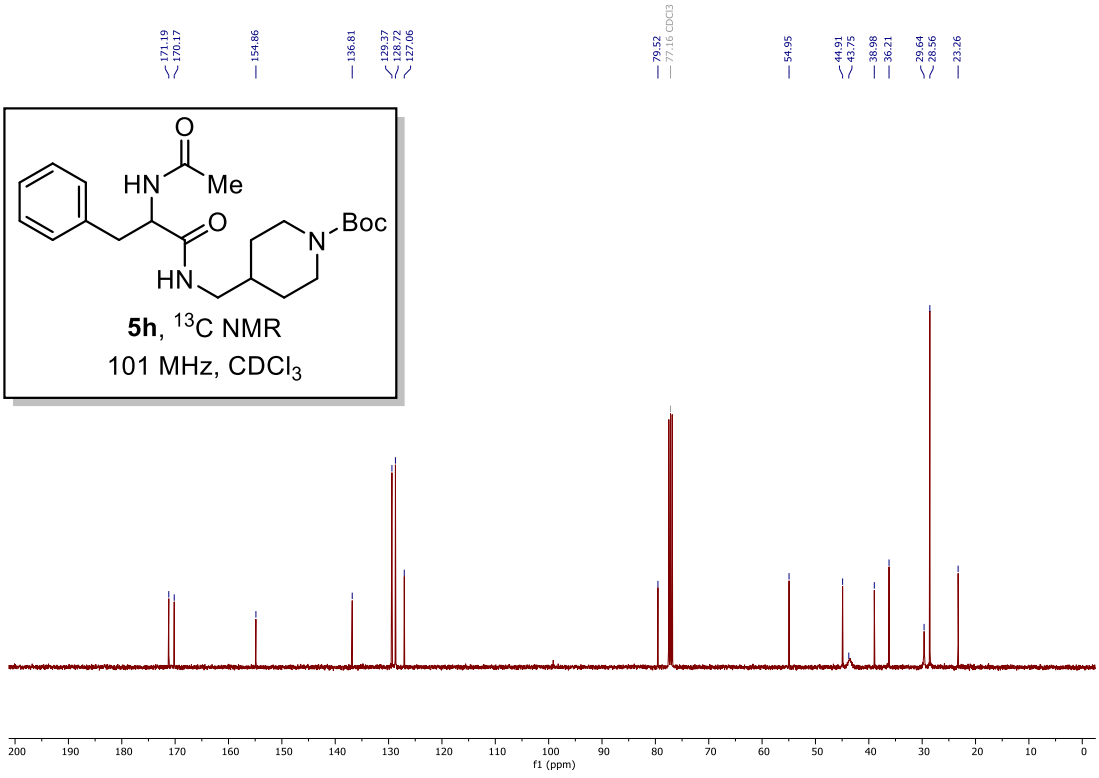

10.07
8.28
8.26
7.64
7.56
7.36
7.35
7.21
7.17
7.10
7.05
7.03
4.69
4.67
4.66
4.65
4.64
4.63
3.04
3.03
3.01
3.00
2.92
2.85
2.83
2.81
2.50 DMSO-d6
1.79
HN
Me
O
O
HN
Ph
5f, 1H NMR
400 MHz, DMSO-d6
0.90
0.88
2.11
6.17
1.08
1.16
1.00
1.00
0.99
3.02
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

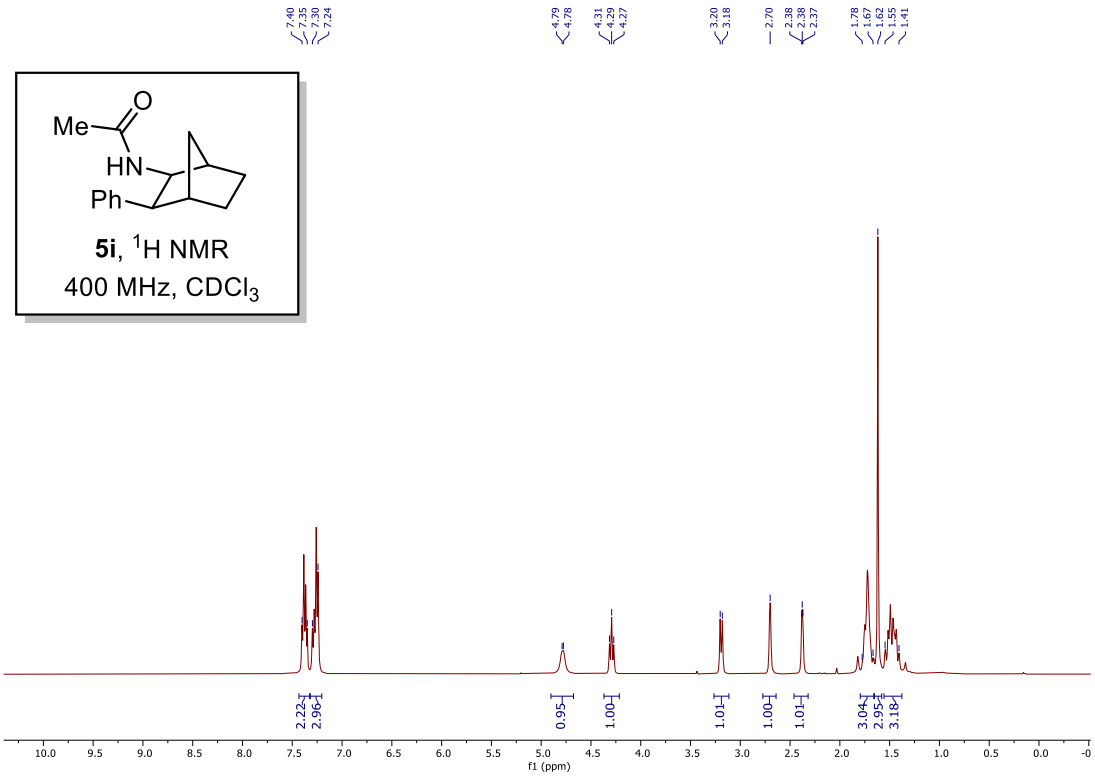

170.34
169.26
138.81
137.72
129.14
128.68
128.06
126.33
123.37
119.34
54.86
39.51 DMSO-d6
37.76
22.39
HN
Me
O
O
HN
Ph
5f, 13C NMR
101 MHz, DMSO-d6
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

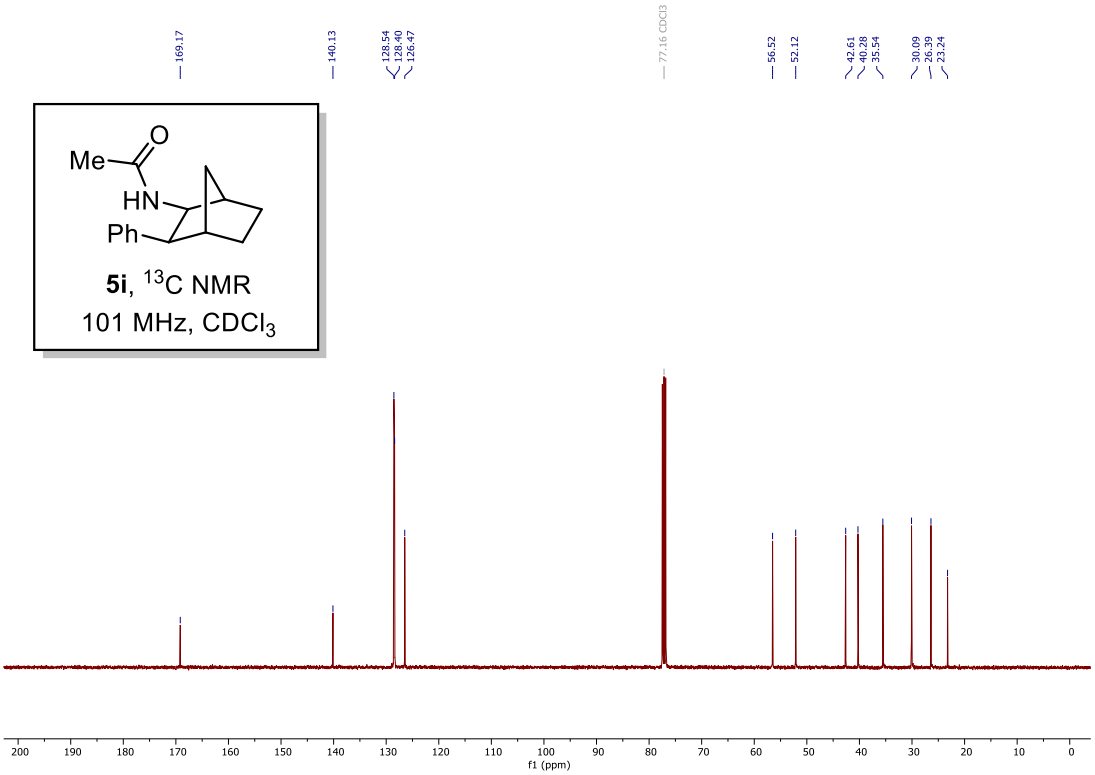

HN
Me
O
O
HN
n-Pent
5g, 1H NMR
400 MHz, CDCl3
f1 (ppm)

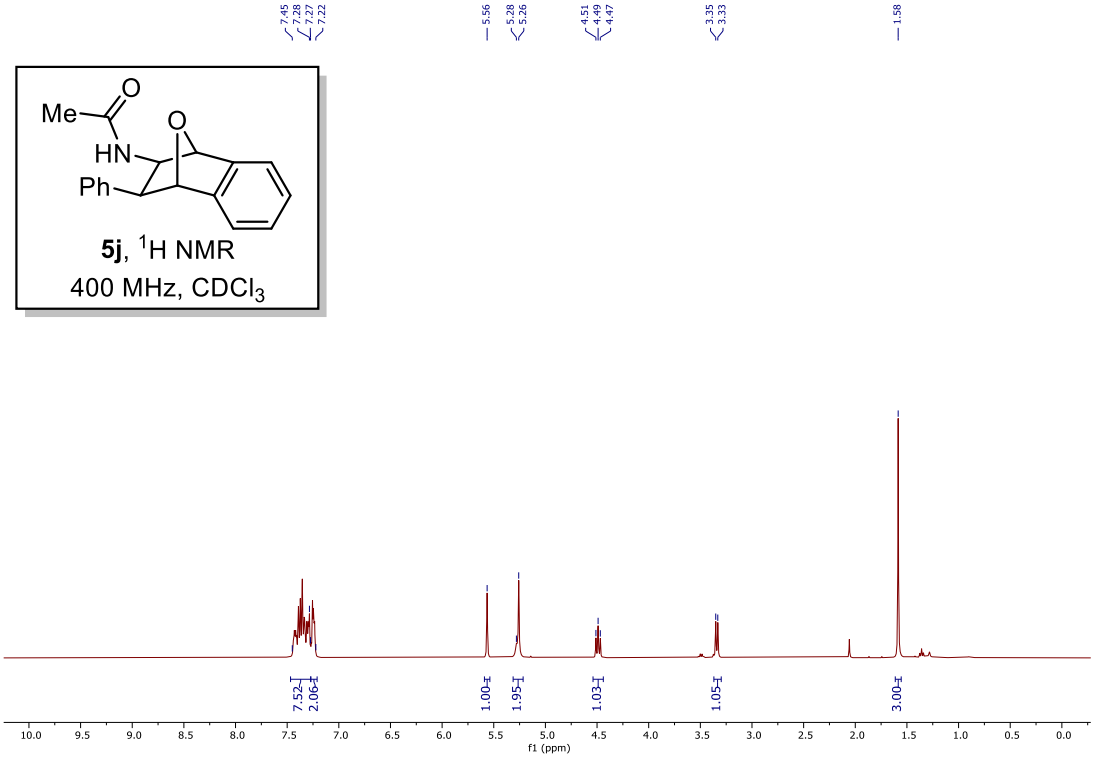

HN
Me
O
O
HN
n-Pent
5g, 13C NMR
101 MHz, CDCl3
f1 (ppm)

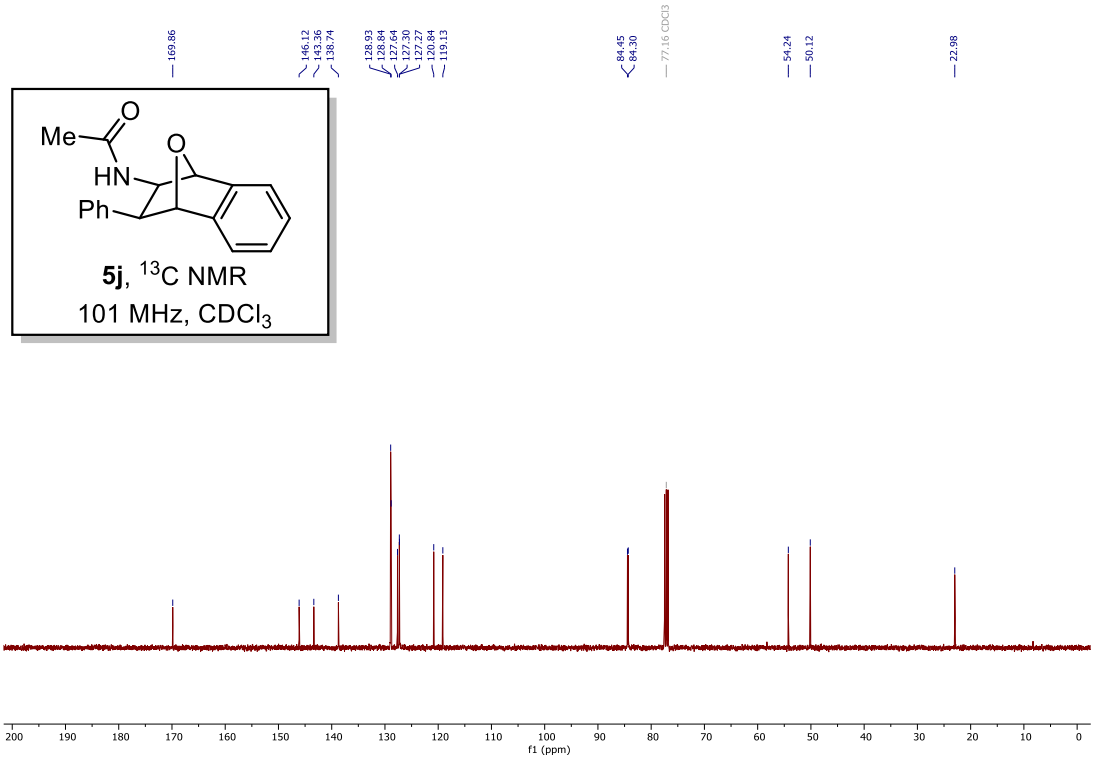

HN
Me
O
O
HN
N
Boc
5h, 1H NMR
400 MHz, CDCl3
f1 (ppm)

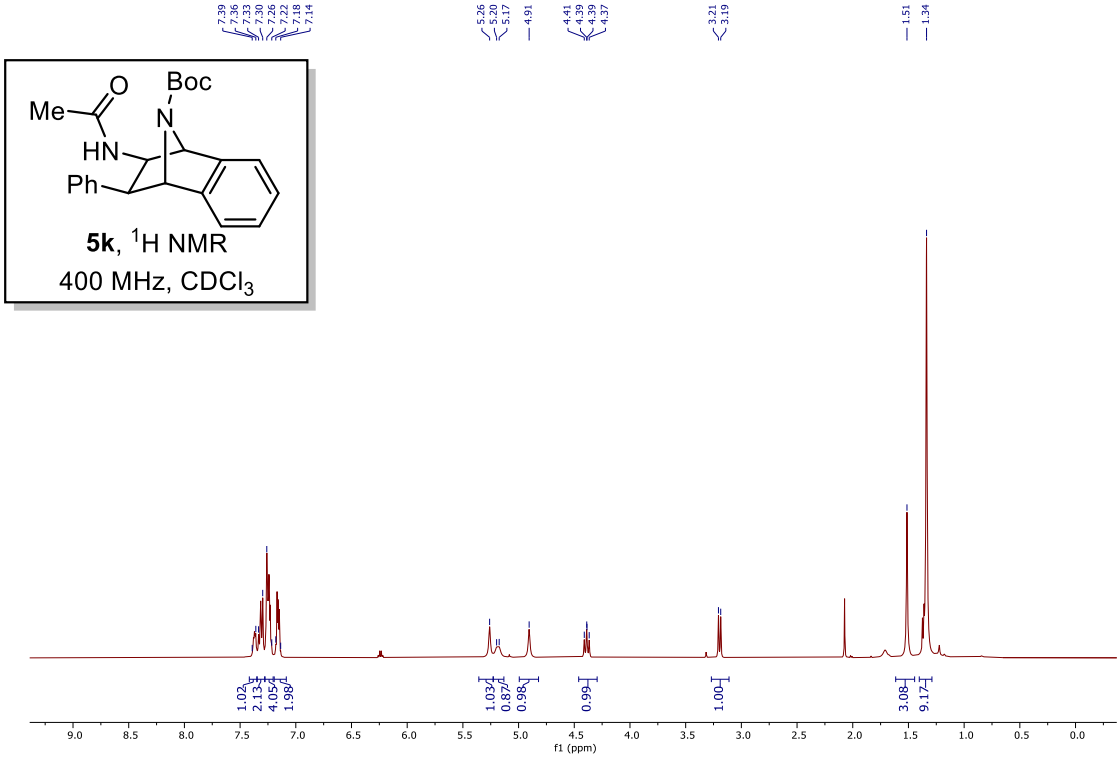

HN
Me
O
O
HN
N
Boc
5h, 13C NMR
101 MHz, CDCl3
f1 (ppm)

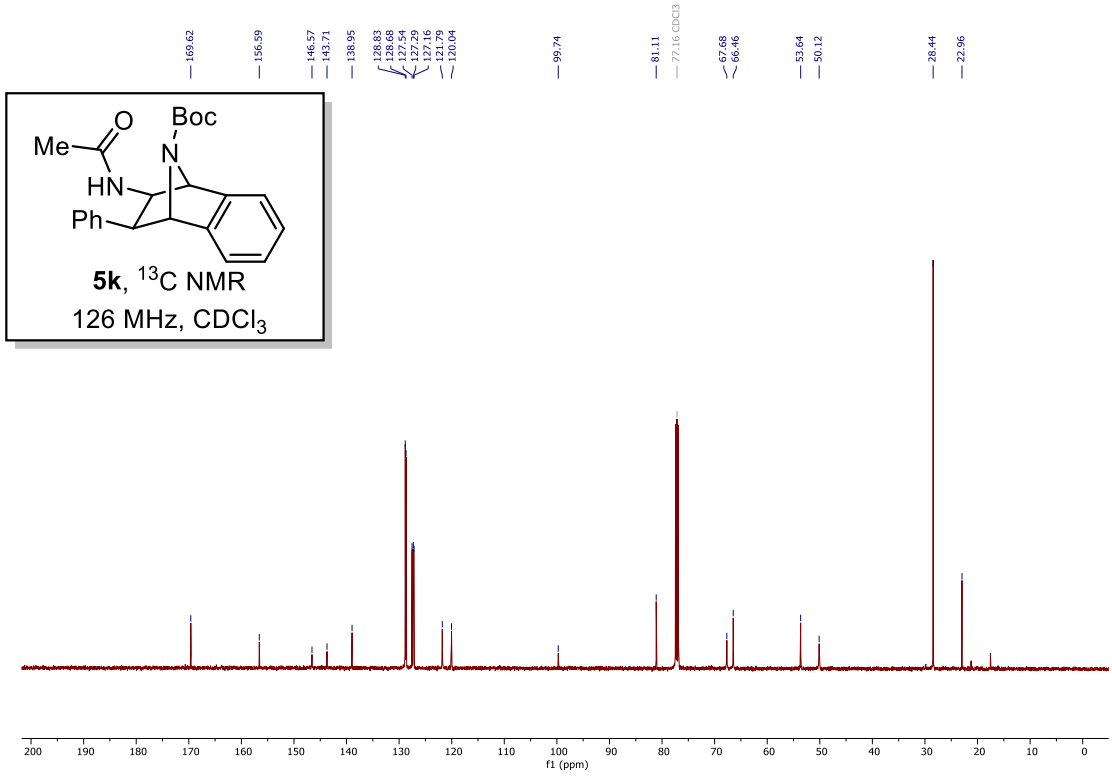

Me
O
HN
Ph
5i, 1H NMR
400 MHz, CDCl3
7.40
7.35
7.30
7.24
4.79
4.78
4.31
4.29
4.27
3.20
3.18
2.70
2.38
2.38
2.37
1.78
1.67
1.62
1.55
1.41
2.22
2.96
0.95
1.00
1.01
1.00
1.01
3.04
2.95
3.18
f1 (ppm)

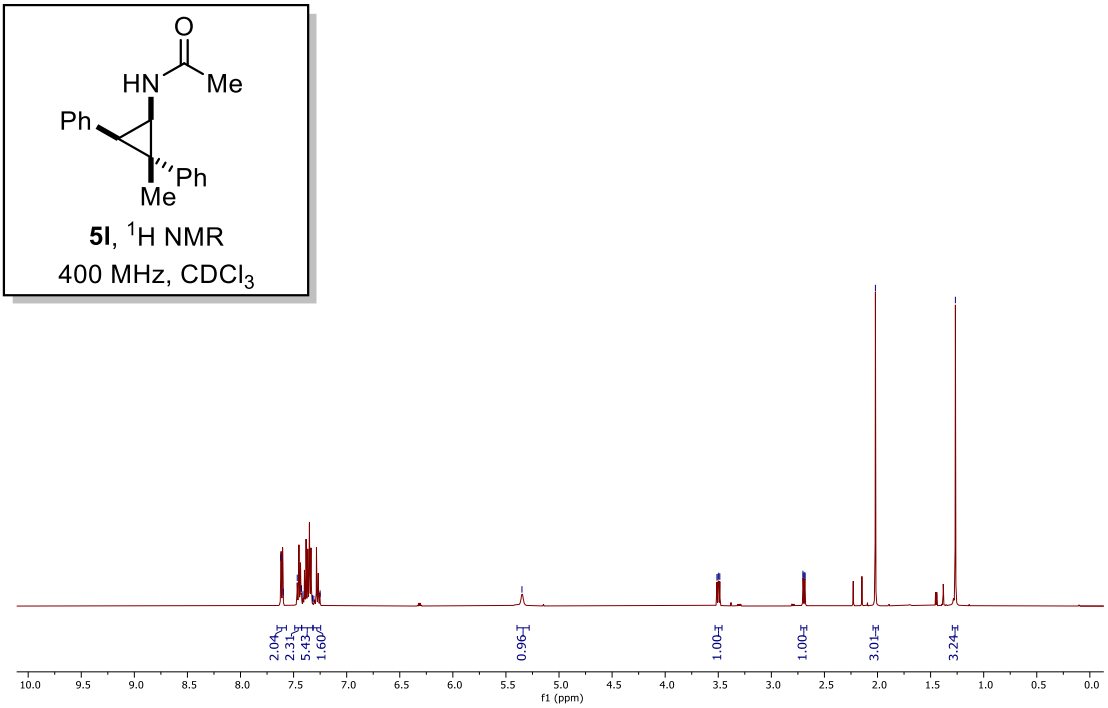

Me
O
HN
Ph
5i, 13C NMR
101 MHz, CDCl3
169.17
140.13
128.54
128.40
126.47
77.16 CDCl3
56.52
52.12
42.61
40.28
35.54
30.09
26.39
23.24
f1 (ppm)

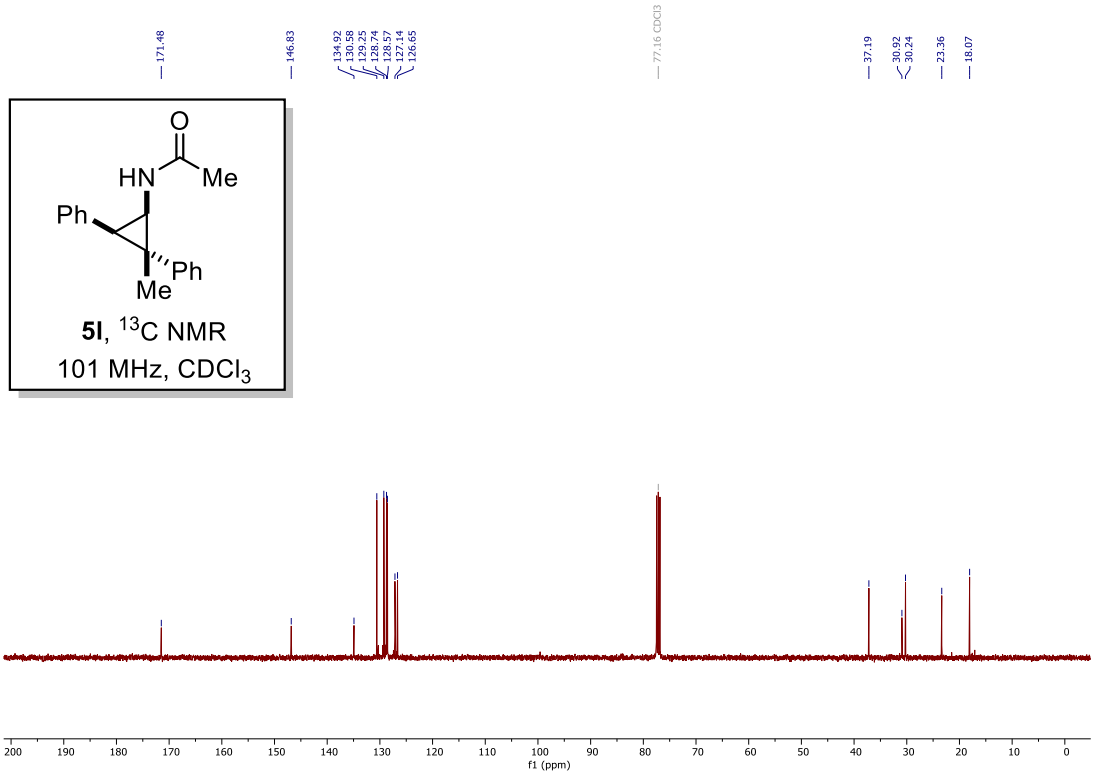

7.45
7.28
7.27
7.22
5.56
5.28
5.26
4.51
4.49
4.47
3.35
3.33
1.58
Me
O
HN
O
Ph
5j, 1H NMR
400 MHz, CDCl3
7.52
2.06
1.00
1.95
1.03
1.05
3.00
f1 (ppm)

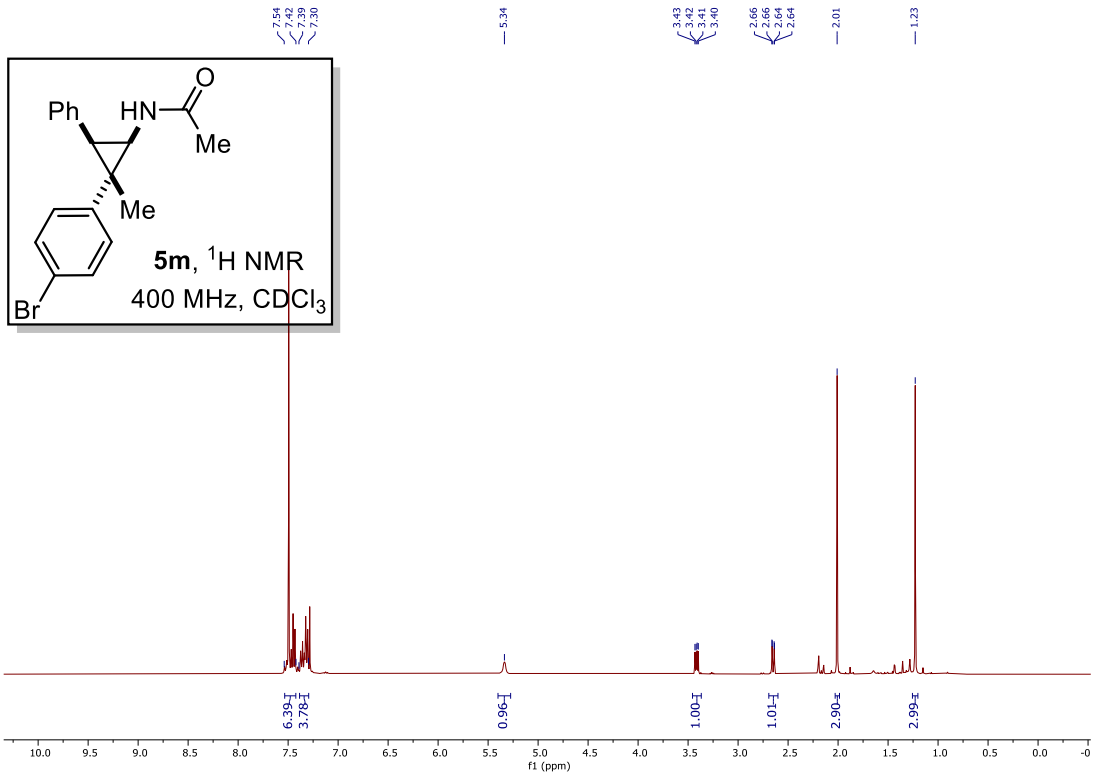

169.86
146.12
143.36
138.74
128.93
128.84
127.64
127.30
127.27
120.84
119.13
84.45
84.30
77.16 CDCl3
54.24
50.12
22.98
Me
O
HN
O
Ph
5j, 13C NMR
101 MHz, CDCl3
f1 (ppm)

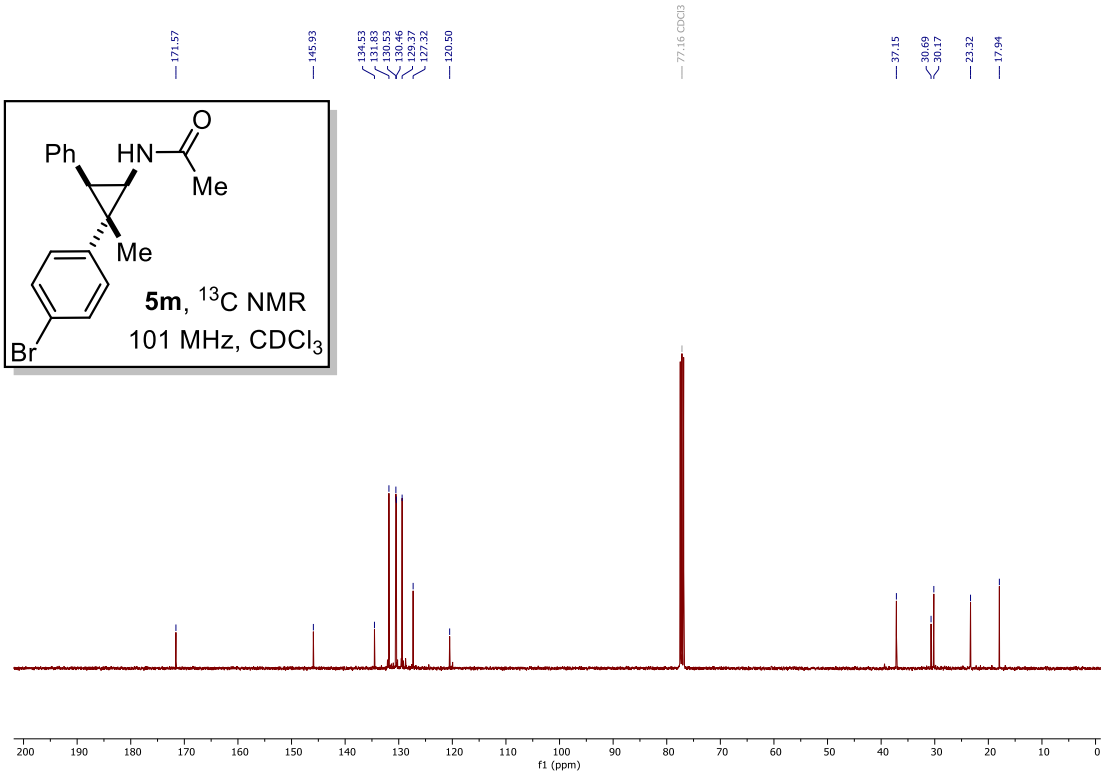

Me
O
Boc
N
HN
Ph
5k, 1H NMR
400 MHz, CDCl3
f1 (ppm)


Me
O
Boc
N
HN
Ph
5k, 13C NMR
126 MHz, CDCl3
f1 (ppm)

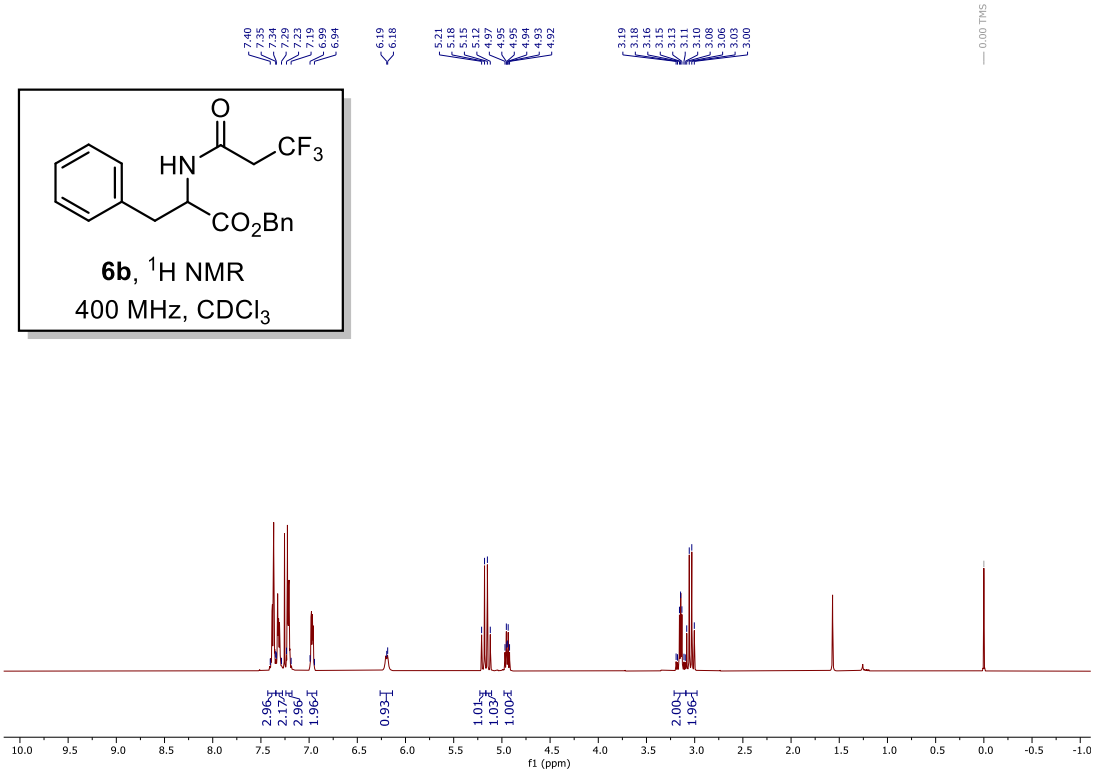

7.62
7.60
7.47
7.43
7.41
7.32
7.31
7.25
5.35
3.51
3.50
3.50
3.49
2.70
2.70
2.69
2.68
2.02
1.27
O
HN
Me
Ph
Ph
Me
5l, 1H NMR
400 MHz, CDCl3
2.04
2.31
5.43
1.60
0.96
1.00
1.00
3.01
3.24
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


171.48
146.83
134.92
130.58
129.25
128.74
128.57
127.14
126.65
77.16 CDCl3
37.19
30.92
30.24
23.36
18.07
O
HN
Me
Ph
Ph
Me
5l, 13C NMR
101 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

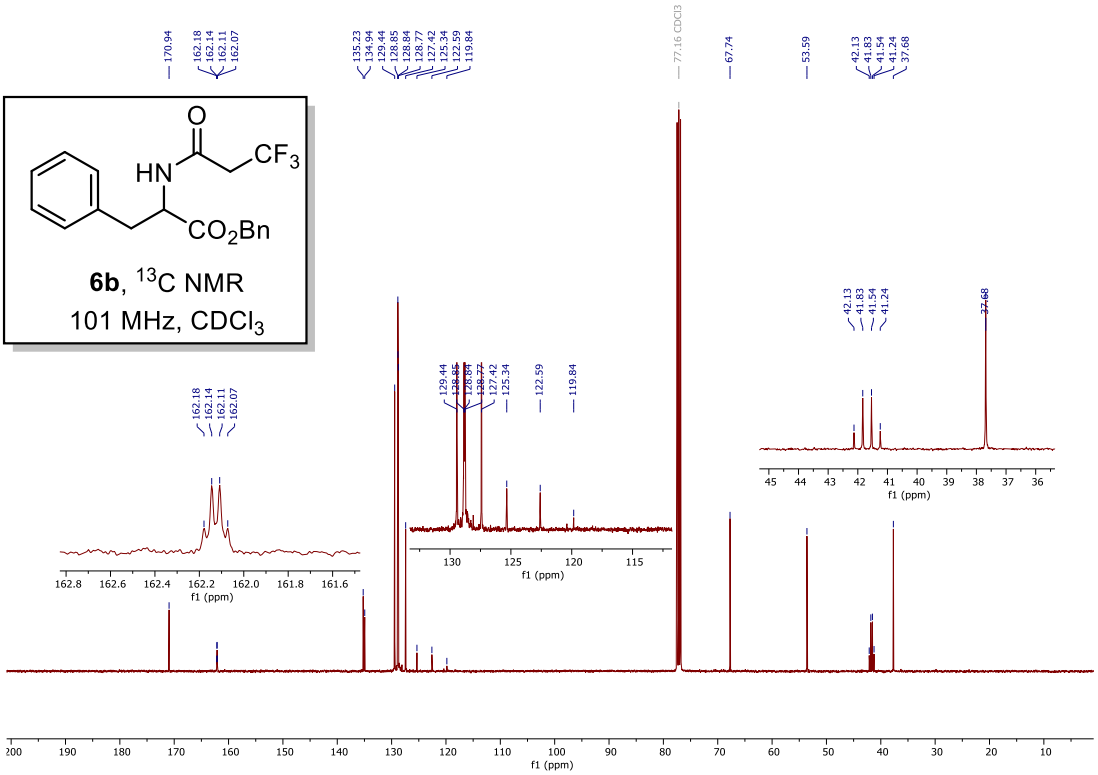

Ph
HN
O
Me
Me
Br
5m, 1H NMR
400 MHz, CDCl3
7.54
7.42
7.39
7.30
5.34
3.43
3.42
3.41
3.40
2.66
2.66
2.64
2.64
2.01
1.23
6.39
3.78
0.96
1.00
1.01
2.90
2.99
f1 (ppm)


Ph
HN
O
Me
Me
Br
5m, 13C NMR
101 MHz, CDCl3
171.57
145.93
134.53
131.83
130.53
130.46
129.37
127.32
120.50
77.16 CDCl3
37.15
30.69
30.17
23.32
17.94
f1 (ppm)

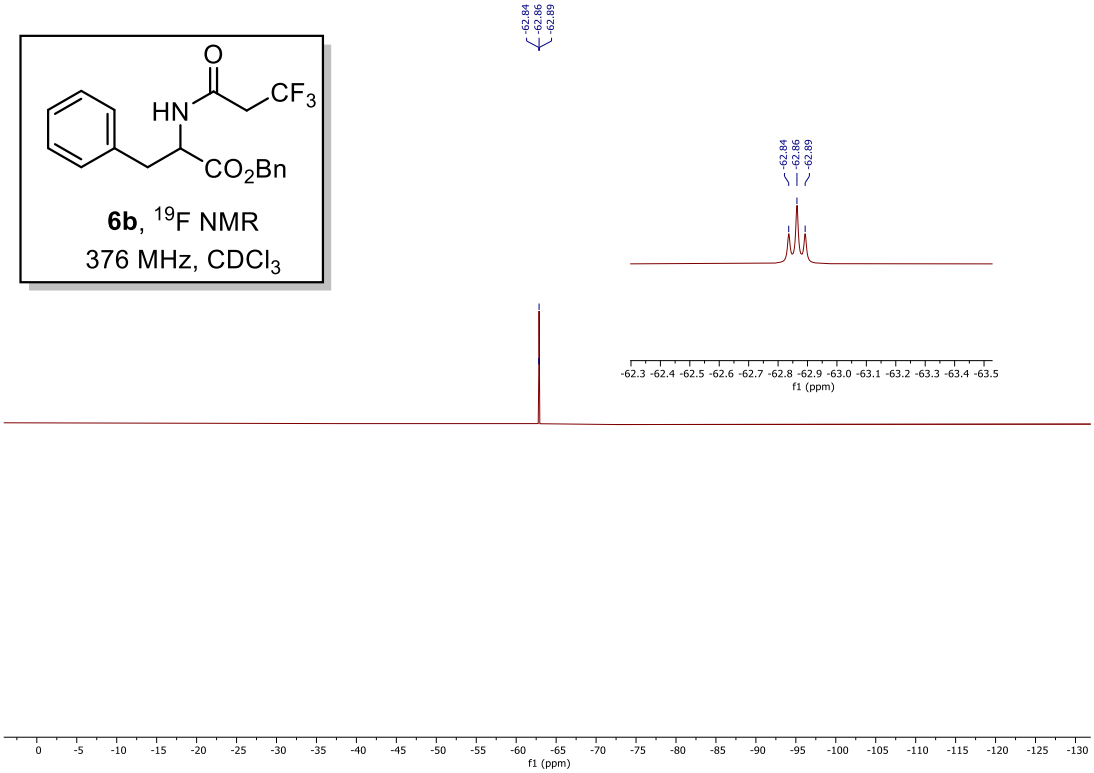
6b, ^{1}H NMR
400 MHz, $CDCl_3$

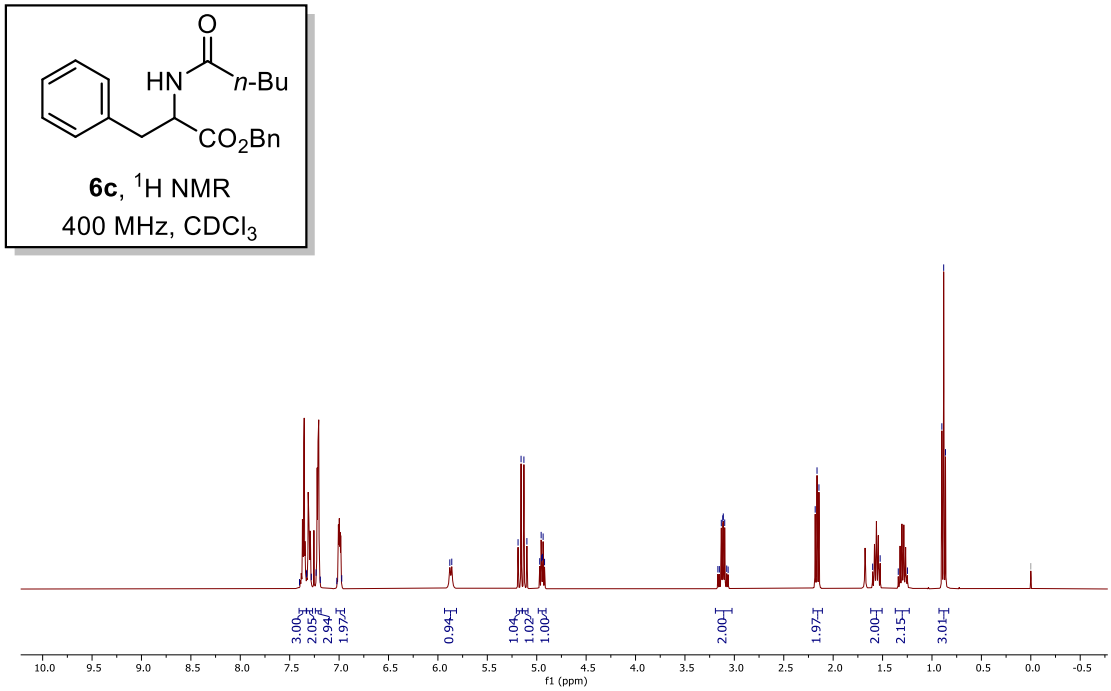


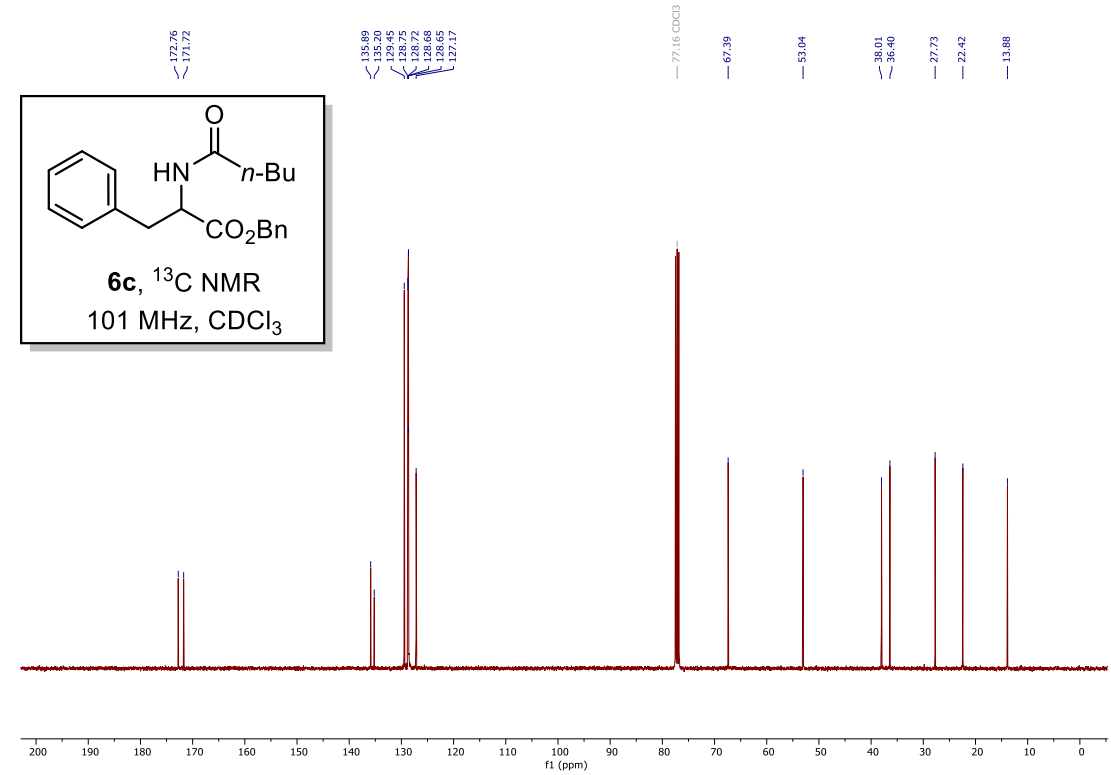
6b, ^{13}C NMR
101 MHz, $CDCl_3$



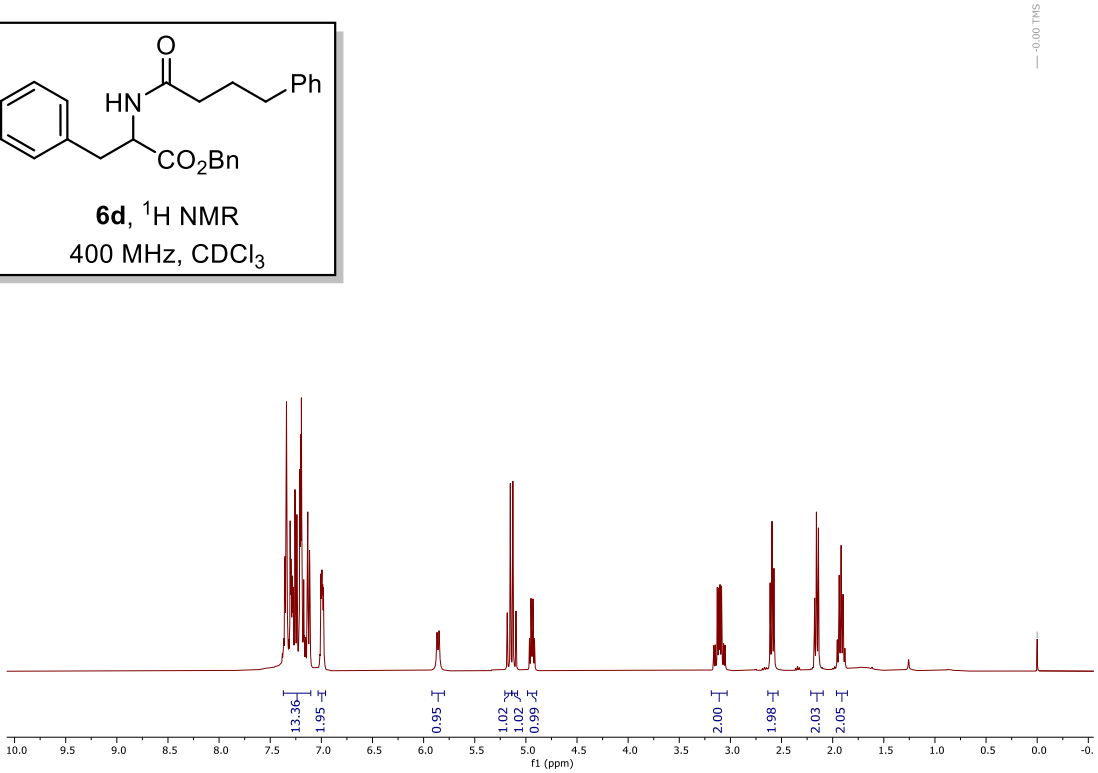
6b, ^{19}F NMR
376 MHz, $CDCl_3$

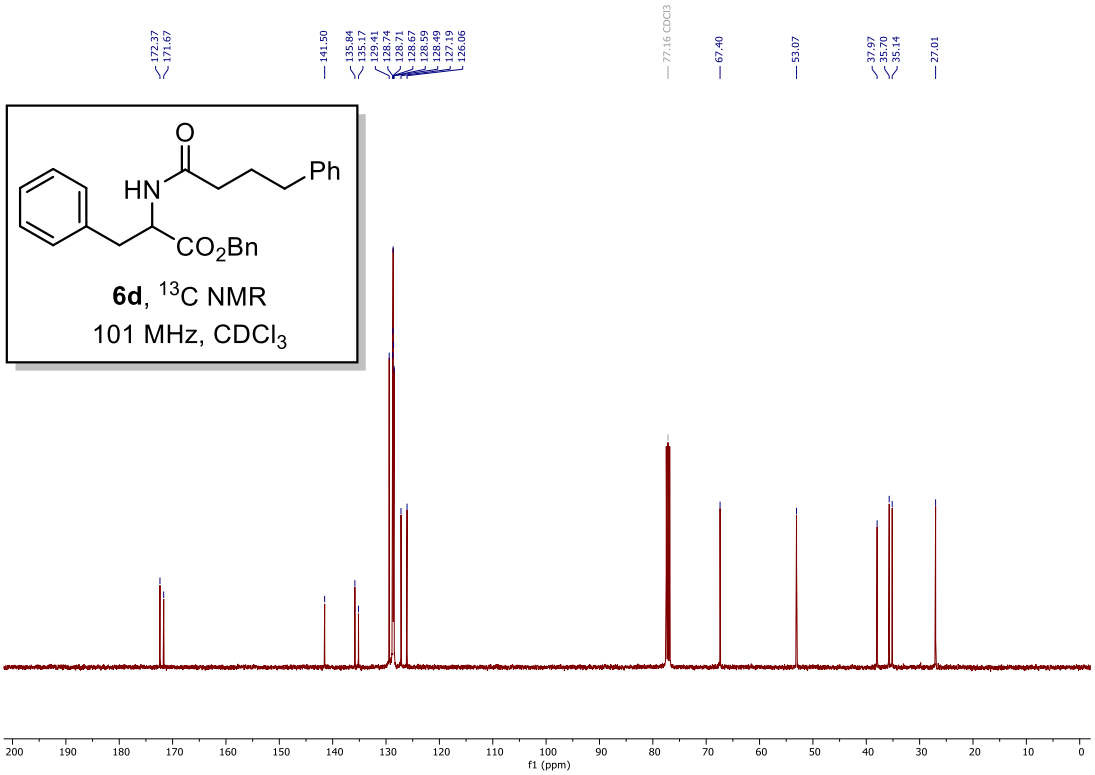



HN
n-Bu
CO2Bn
6c, 1H NMR
400 MHz, CDCl3
f1 (ppm)

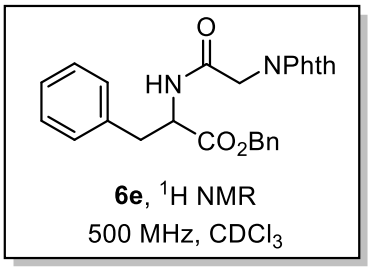

HN
n-Bu
CO2Bn
6c, 13C NMR
101 MHz, CDCl3
f1 (ppm)

6d, ^{1}H NMR
400 MHz, $CDCl_3$

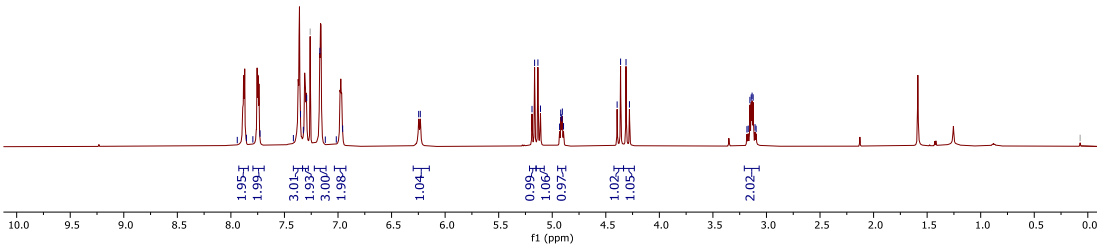


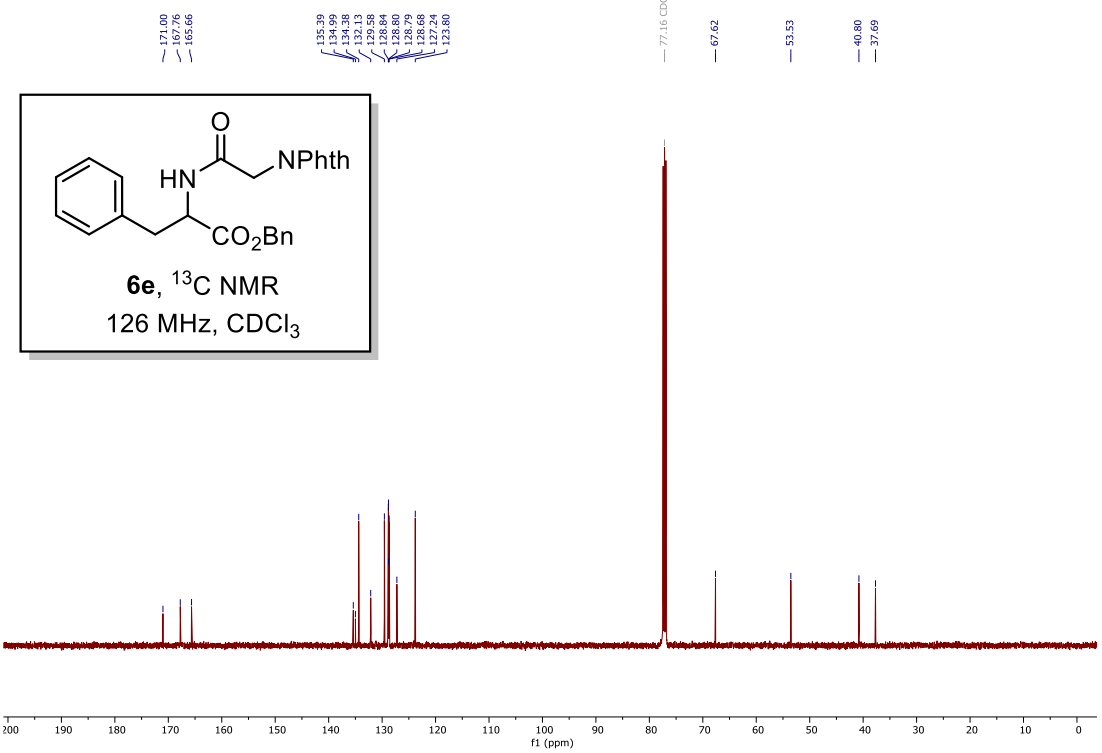


6d, ^{13}C NMR
101 MHz, $CDCl_3$

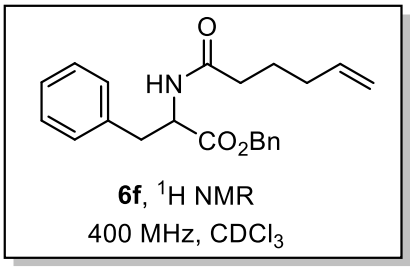


6e, ^{1}H NMR
500 MHz, $CDCl_3$

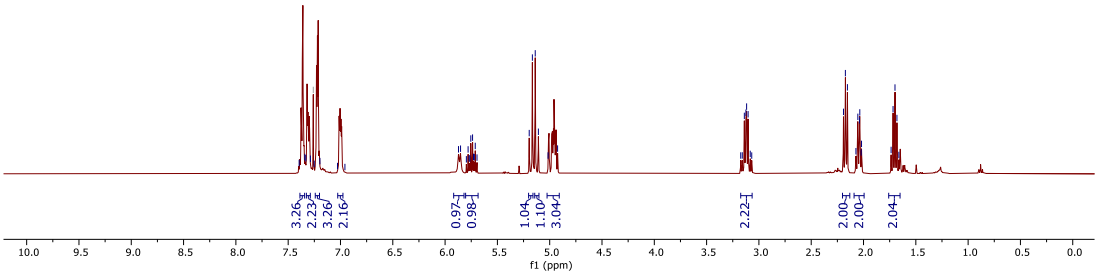


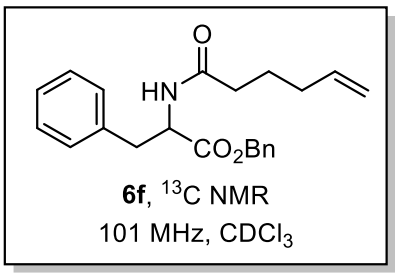


6e, ^{13}C NMR
126 MHz, $CDCl_3$

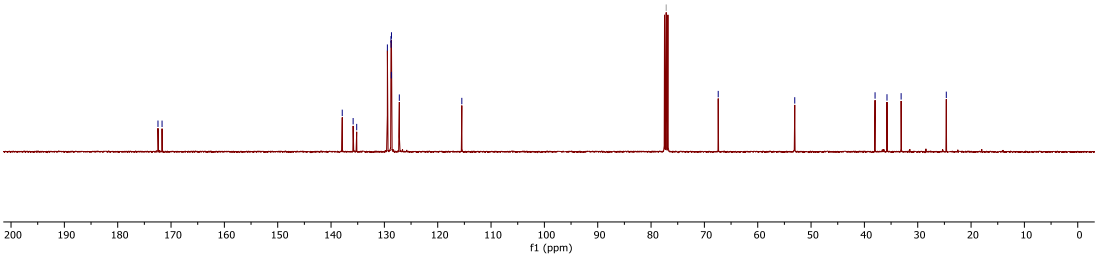


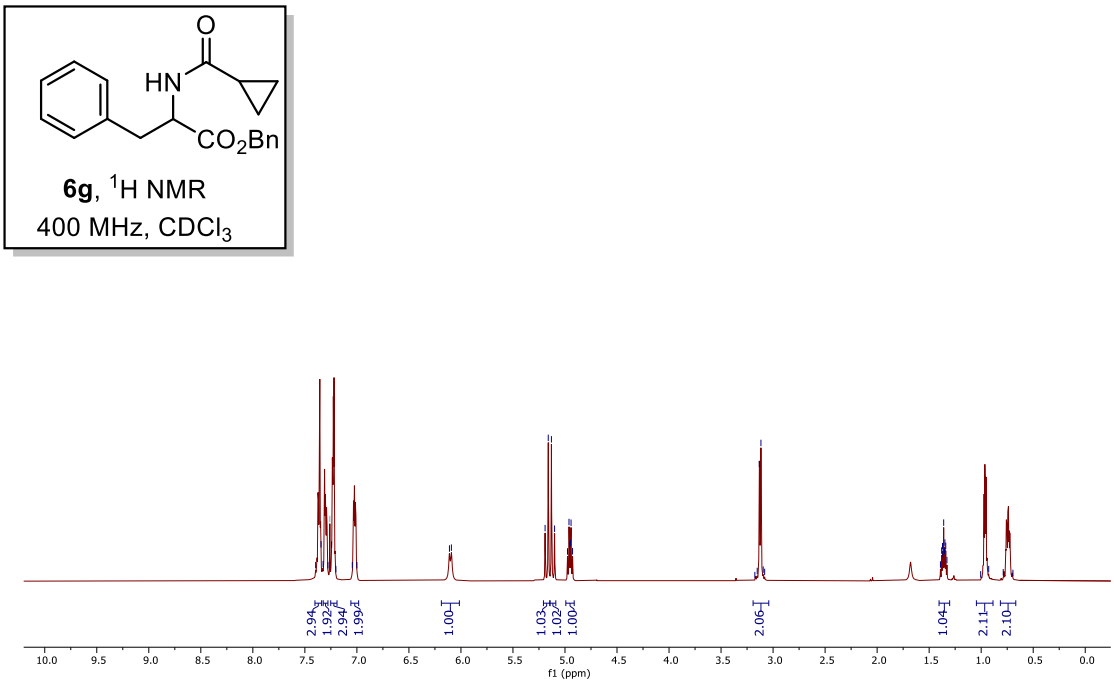
6f, ^{1}H NMR
400 MHz, $CDCl_3$

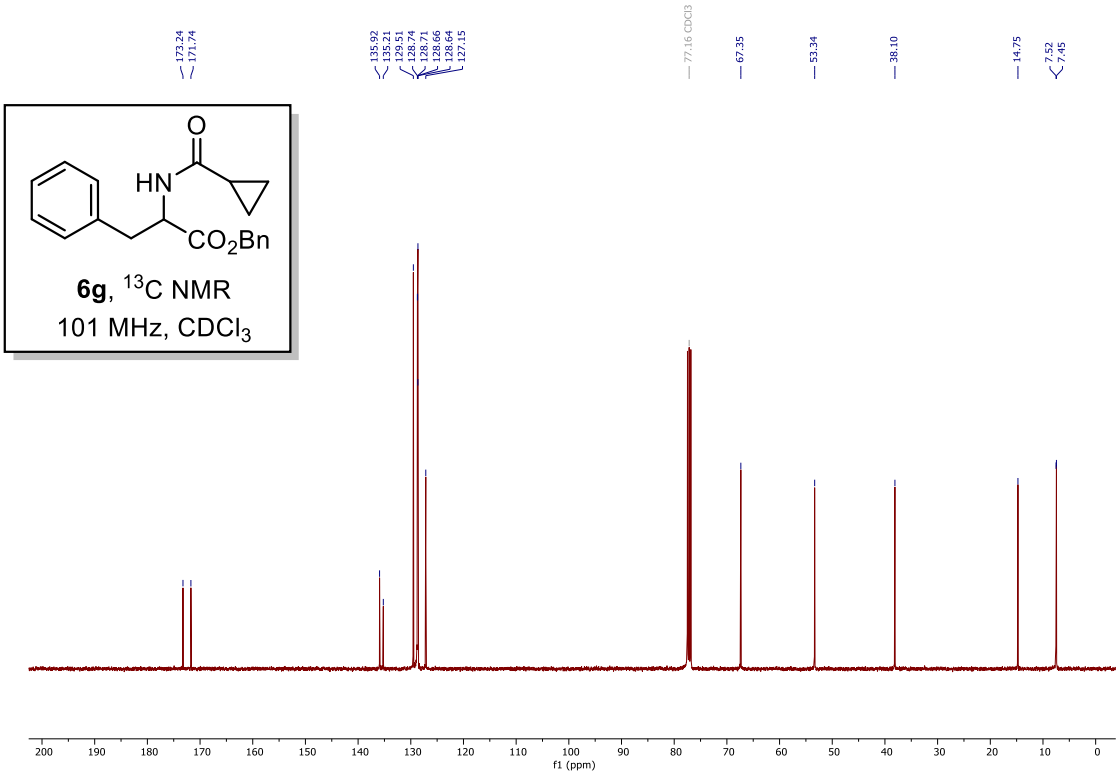


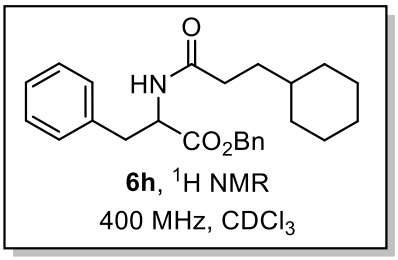


6f, ^{13}C NMR
101 MHz, $CDCl_3$

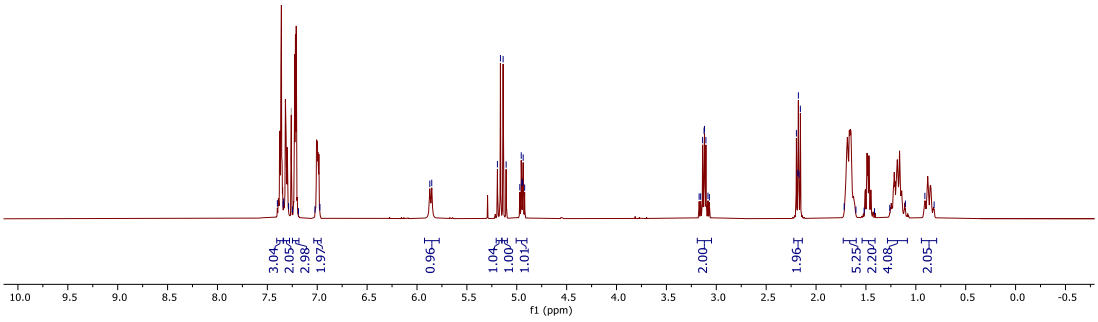


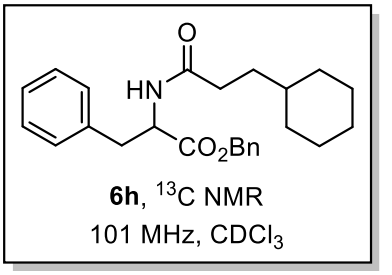

O
HN
CO2Bn
6g, 1H NMR
400 MHz, CDCl3
f1 (ppm)


O
HN
CO2Bn
6g, 13C NMR
101 MHz, CDCl3
f1 (ppm)

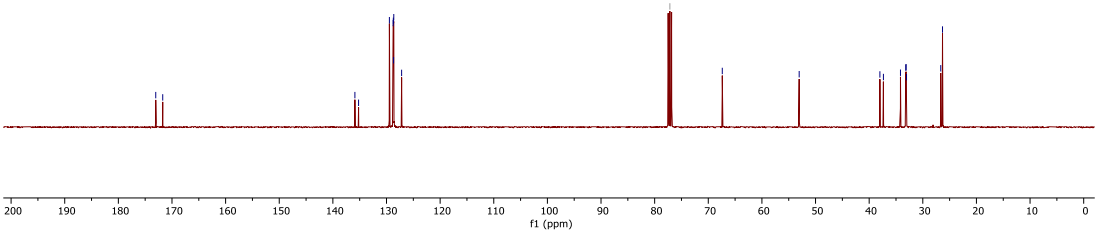


6h, ^{1}H NMR
400 MHz, $CDCl_3$





6h, ^{13}C NMR
101 MHz, $CDCl_3$



Appendix D

SUPPLEMENTARY DATA FOR CHAPTER FIVE

Rhodium(III)-Catalyzed Three-Component 1,2-Diamination of Unactivated Terminal Alkenes

Author: Sumin Lee, Young Jin Jang, Erik J. T. Phipps, Honghui Lei, Tomislav Rovis
Publication: Synthesis
Publisher: Georg Thieme Verlag KG
Date: Jan 1, 2020

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Licensed Content Author	Sumin Lee, Young Jin Jang, Erik J. T. Phipps, Honghui Lei, Tomislav Rovis
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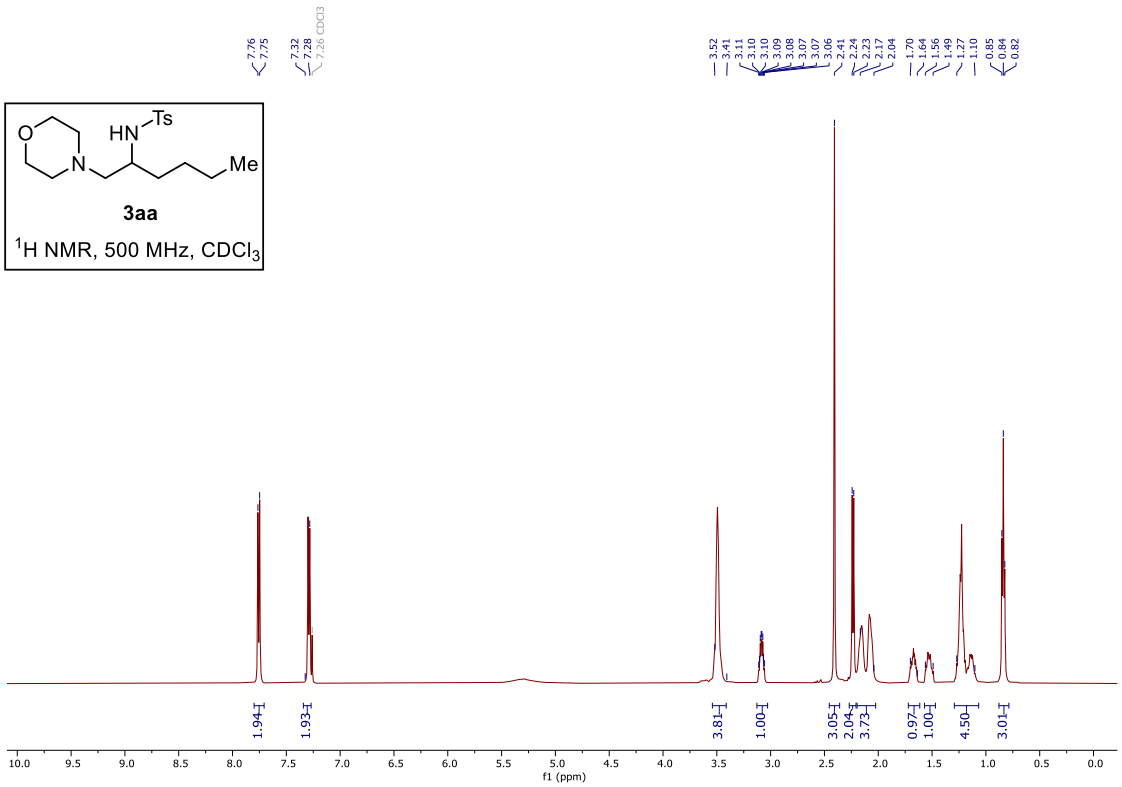
Supporting Information

Rhodium(III)-Catalyzed Three-Component 1,2-Diamination of Unactivated Terminal Alkenes

Sumin Lee, Young Jin Jang, Erik J. T. Phipps, Honghui Lei and Tomislav Rovis*

Department of Chemistry, Columbia University, New York, New York 10027

Contents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7.75
7.32
7.28
7.26 CDCl3
3.52
3.44
3.11
3.10
3.09
3.08
3.07
3.07
3.06
2.41
2.24
2.23
2.17
2.04
1.70
1.64
1.55
1.49
1.27
1.10
0.85
0.84
0.82
O
N
HN
Ts
Me
3aa
1H NMR, 500 MHz, CDCl3
1.94
1.93
3.81
1.00
3.05
2.04
3.73
0.97
1.00
4.50
3.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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2.0
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1.0
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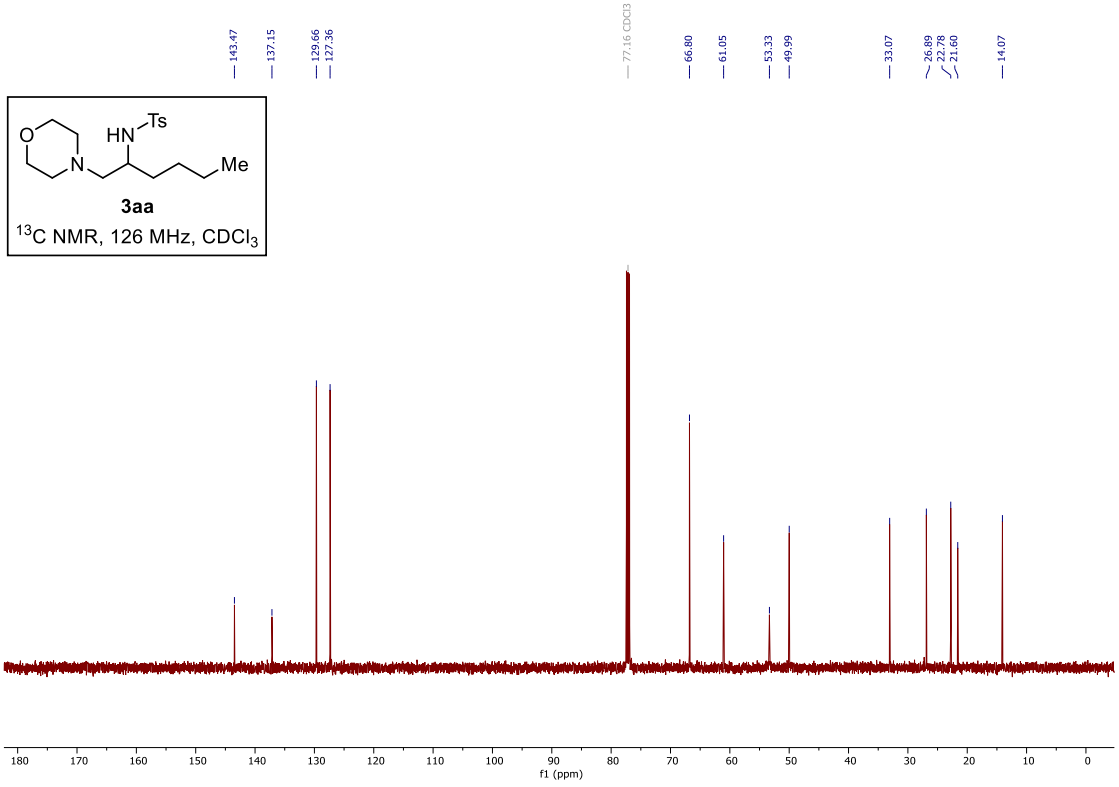
0.0
f1 (ppm)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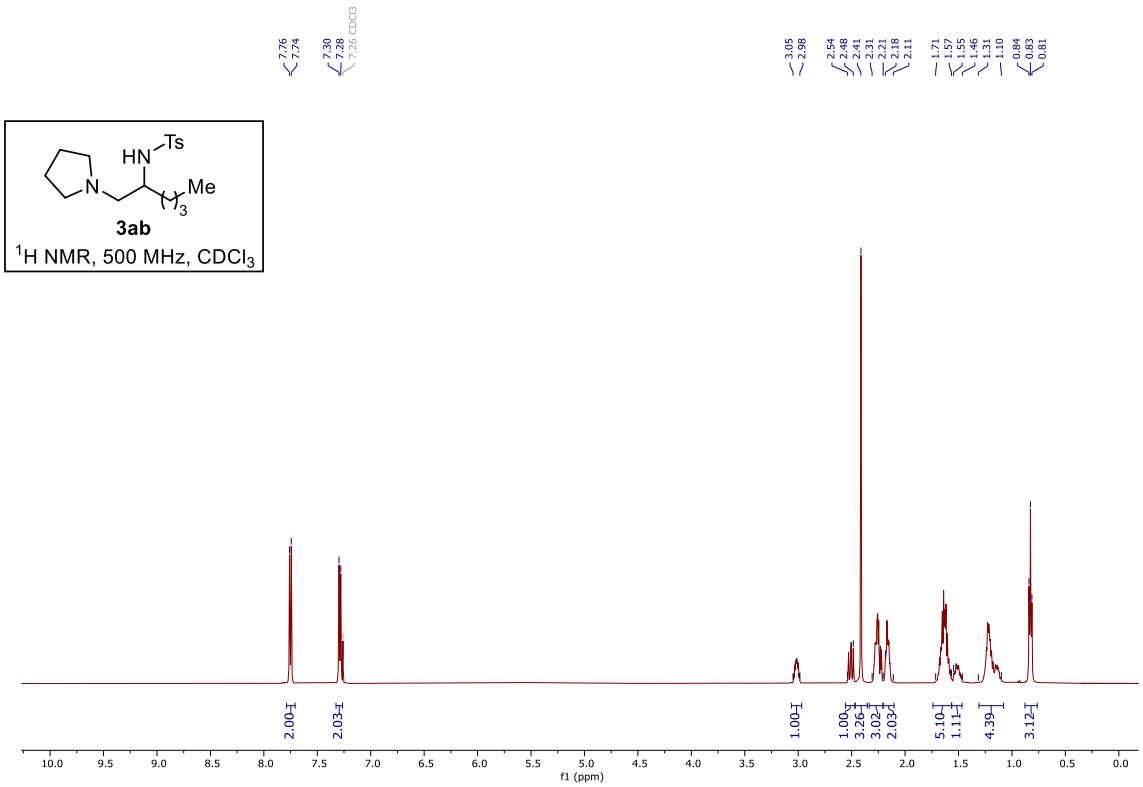
129.66
127.36
77.16 CDCl3
66.80
61.05
53.33
49.99
33.07
26.89
22.78
21.60
14.07
O
N
HN
Ts
Me
3aa
13C NMR, 126 MHz, CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.30
7.28
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2.98
2.54
2.48
2.41
2.31
2.21
2.18
2.11
1.71
1.57
1.55
1.46
1.31
1.10
0.84
0.83
0.81
HN
Ts
N
Me
3
3ab
1H NMR, 500 MHz, CDCl3
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1.00
1.00
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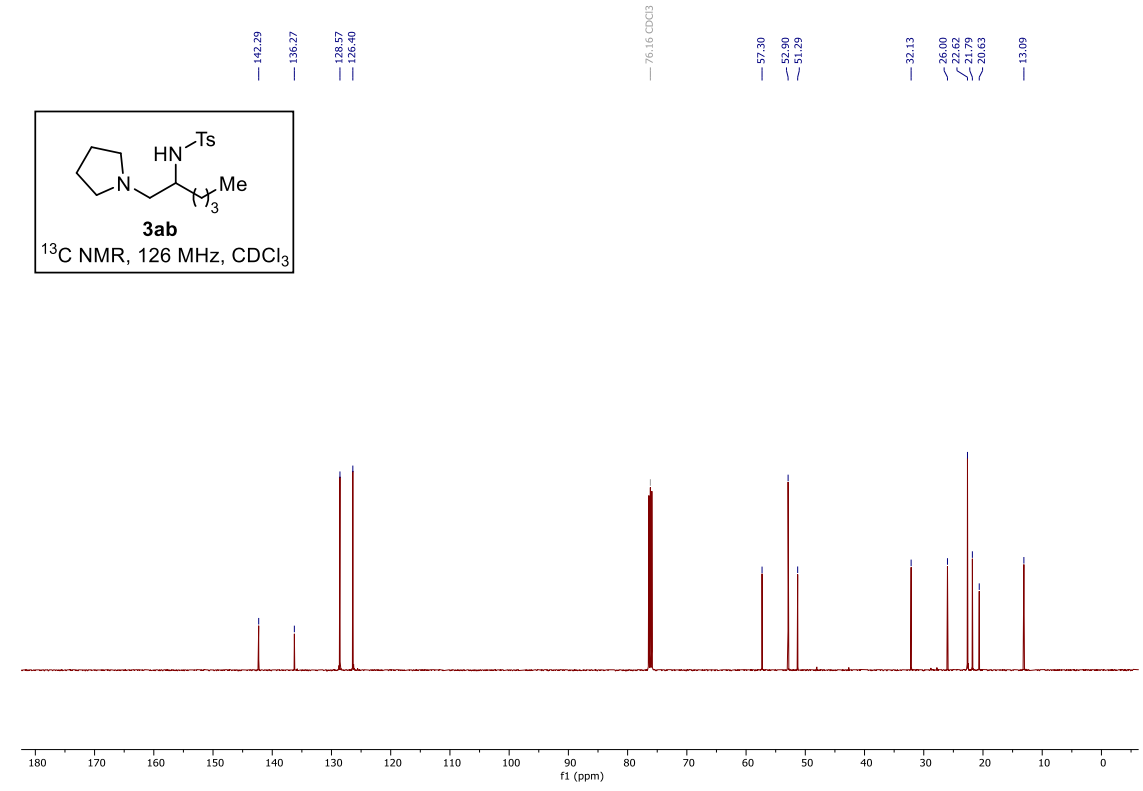
2.03
5.10
1.11
4.39
3.12
f1 (ppm)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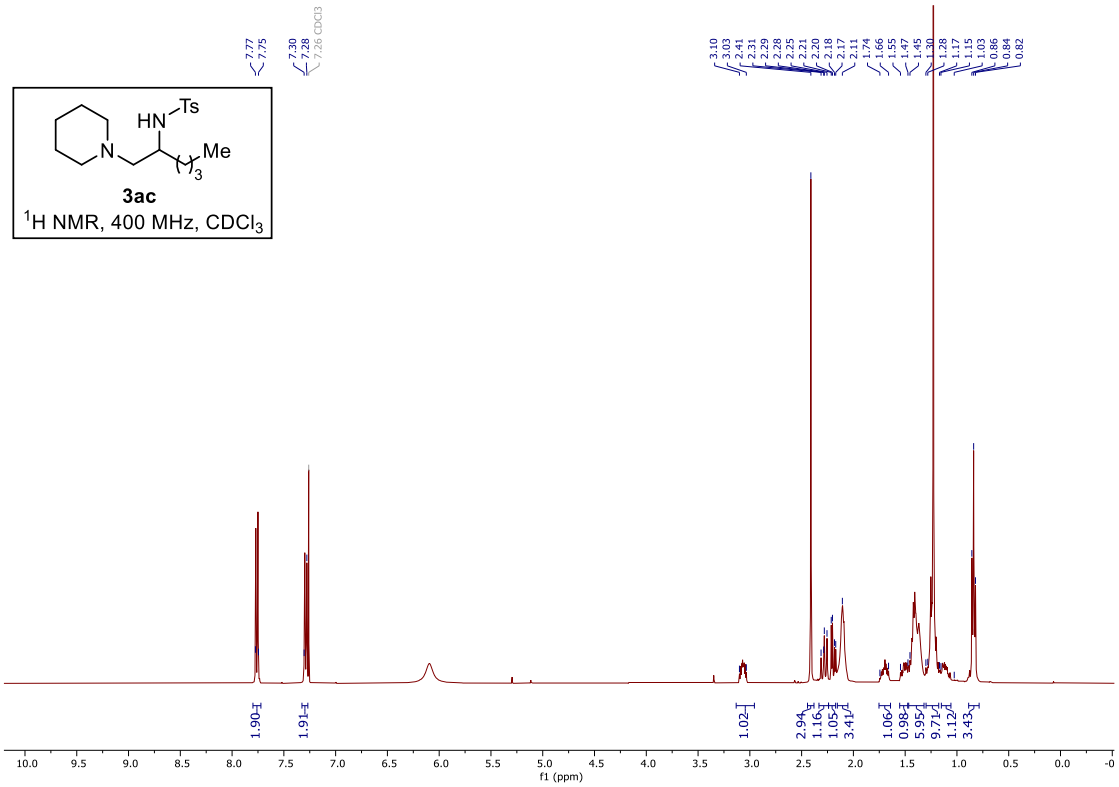
136.27
128.57
126.40
76.16 CDCl3
57.30
52.90
51.29
32.13
26.00
22.62
21.79
20.63
13.09
HN
Ts
N
Me
3
3ab
13C NMR, 126 MHz, CDCl3
f1 (ppm)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7.75
7.30
7.28
7.26 CDCl3
3.10
3.03
2.41
2.31
2.29
2.28
2.25
2.21
2.20
2.18
2.17
2.11
1.74
1.66
1.55
1.47
1.45
1.30
1.28
1.17
1.15
1.03
0.86
0.84
0.82
HN
Ts
N
Me
3
3ac
1H NMR, 400 MHz, CDCl3
1.90
1.91
1.02
2.94
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1.06
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1.12
3.43
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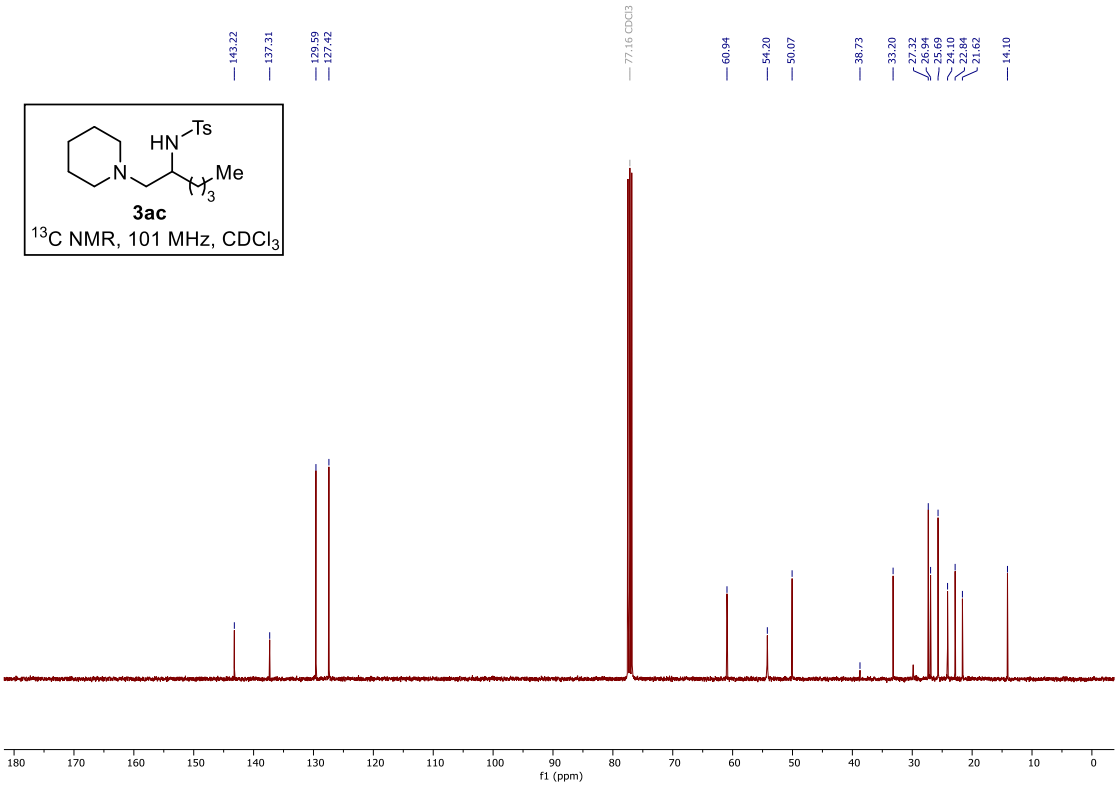
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50.07
38.73
33.20
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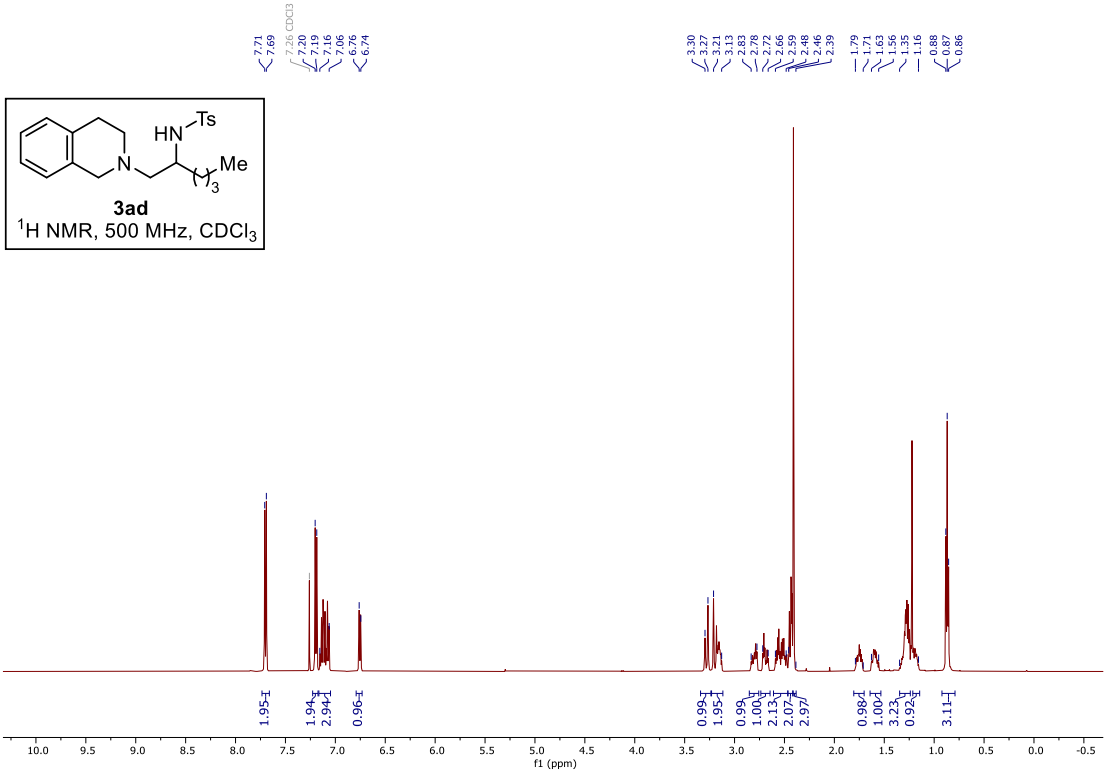
26.94
25.69
24.10
22.84
21.62
14.10
HN
Ts
N
Me
3
3ac
13C NMR, 101 MHz, CDCl3
f1 (ppm)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7.20
7.19
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6.75
6.74
3.30
3.27
3.21
3.13
2.83
2.78
2.72
2.66
2.59
2.48
2.46
2.39
1.79
1.71
1.63
1.56
1.35
1.16
0.88
0.87
0.86
HN
Ts
N
Me
3
3ad
1H NMR, 500 MHz, CDCl3
1.95
1.94
2.94
0.96
0.99
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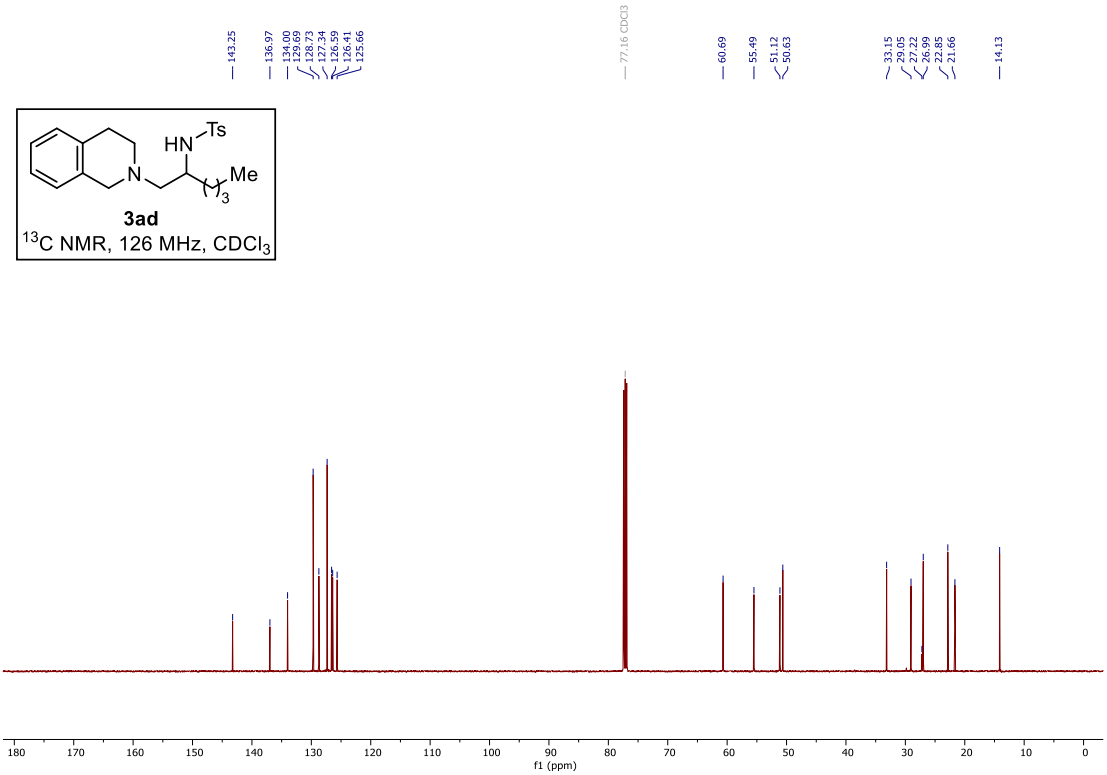
f1 (ppm)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127.34
126.59
126.41
125.66
77.16 CDCl3
60.69
55.49
51.12
50.63
33.15
29.05
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14.13
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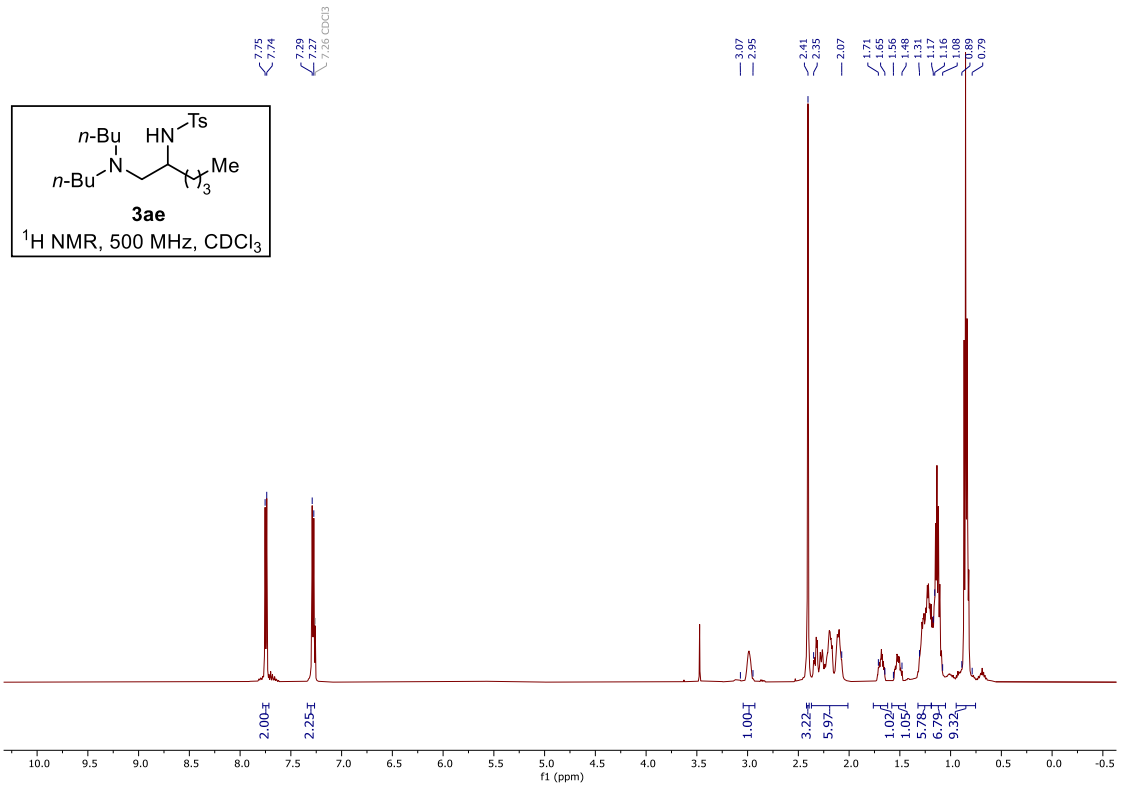
Me
3
3ad
13C NMR, 126 MHz, CDCl3
f1 (ppm)


n-Bu
HN
Ts
N
n-Bu
Me
3
3ae
1H NMR, 500 MHz, CDCl3
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7.74
7.29
7.27
7.26 CDCl3
3.07
2.95
2.41
2.35
2.07
1.71
1.65
1.56
1.48
1.31
1.17
1.16
1.08
0.89
0.79
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2.25
1.00
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1.02
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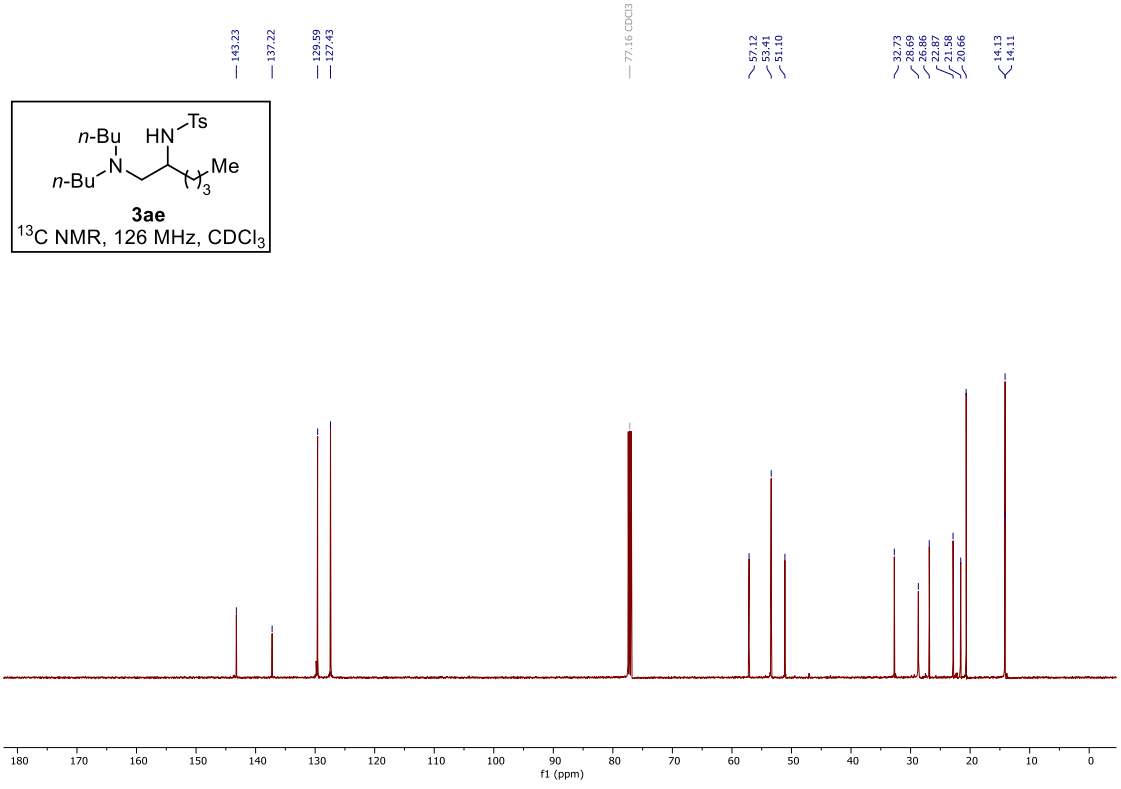
5.78
6.79
9.32
f1 (ppm)


n-Bu
HN
Ts
N
n-Bu
Me
3
3ae
13C NMR, 126 MHz, CDCl3
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137.22
129.59
127.43
77.16 CDCl3
57.12
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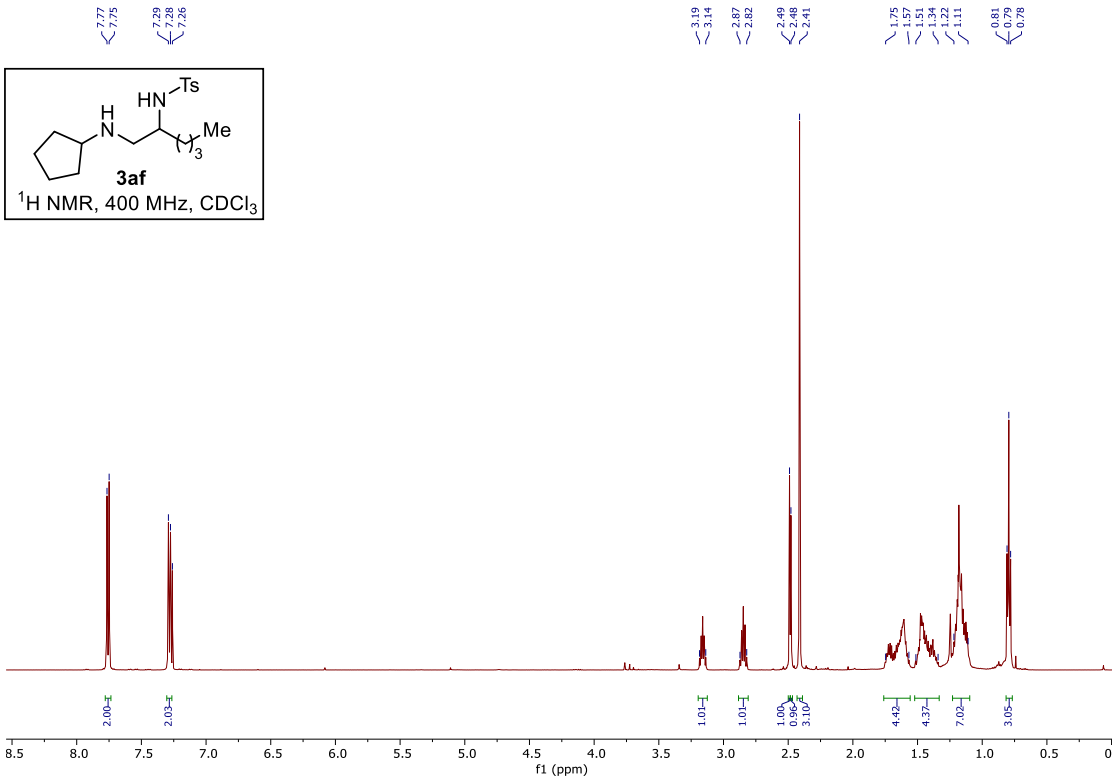
14.11
f1 (ppm)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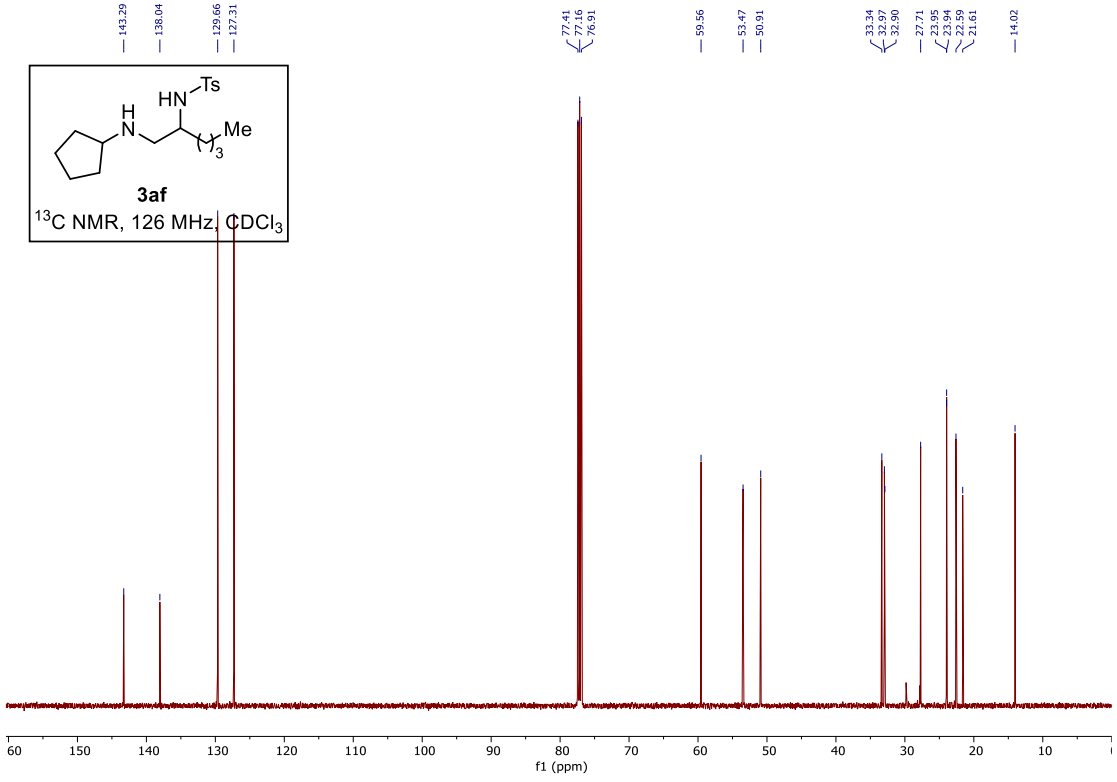
f1 (ppm)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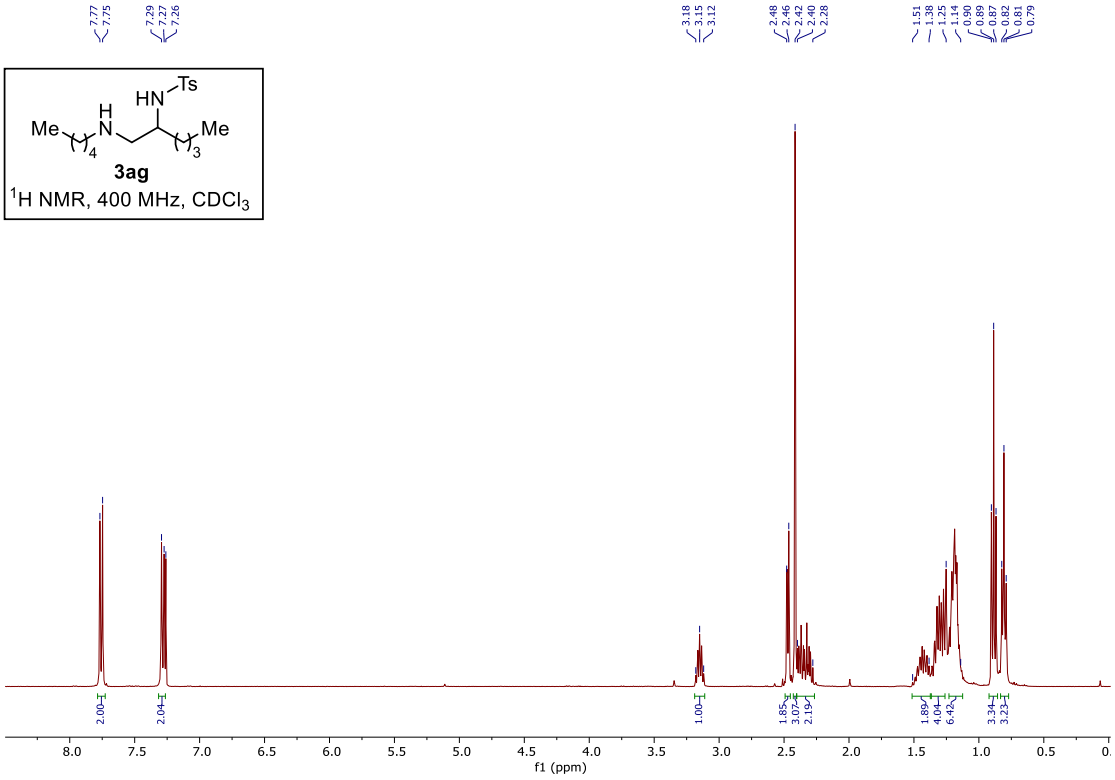
f1 (ppm)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1.51
1.38
1.25
1.14
0.90
0.89
0.87
0.82
0.81
0.79
HN
Ts
H
N
Me
Me
4
3
3ag
1H NMR, 400 MHz, CDCl3
2.00
2.04
1.00
1.85
3.07
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1.89
4.04
6.42
3.34
3.23
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7.5
7.0
6.5
6.0
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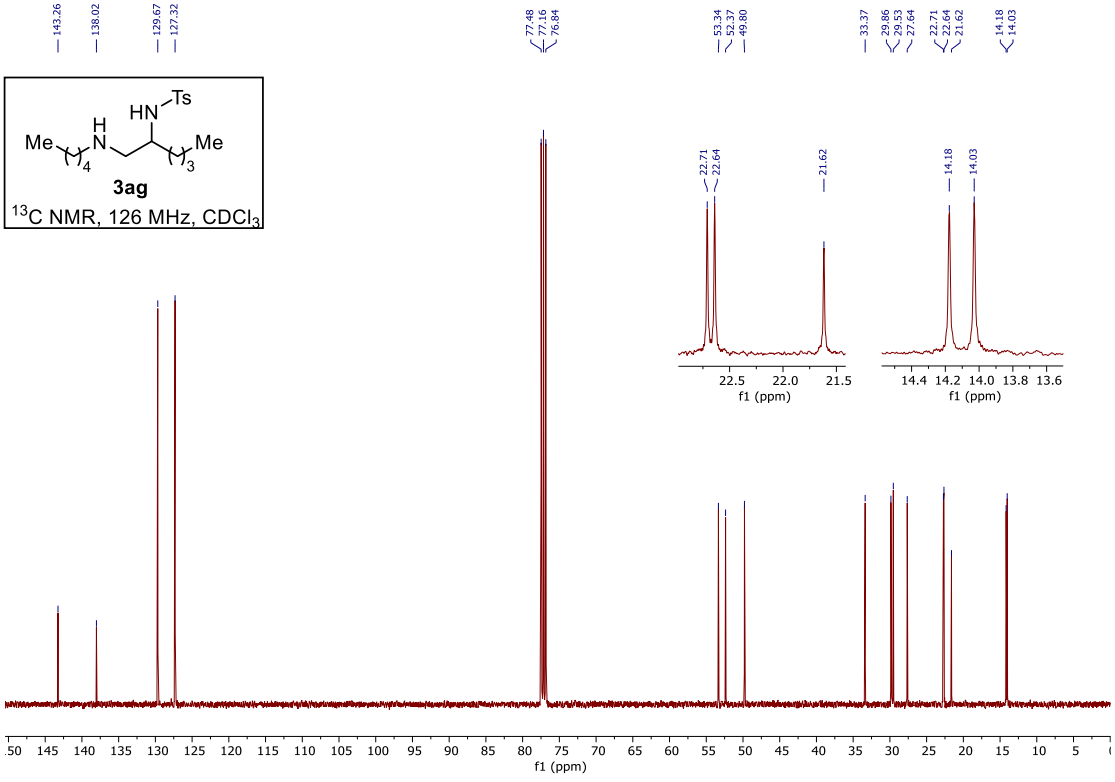
0.5
f1 (ppm)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27.64
22.71
22.64
21.62
14.18
14.03
HN
Ts
H
N
Me
Me
4
3
3ag
13C NMR, 126 MHz, CDCl3
22.71
22.64
21.62
14.18
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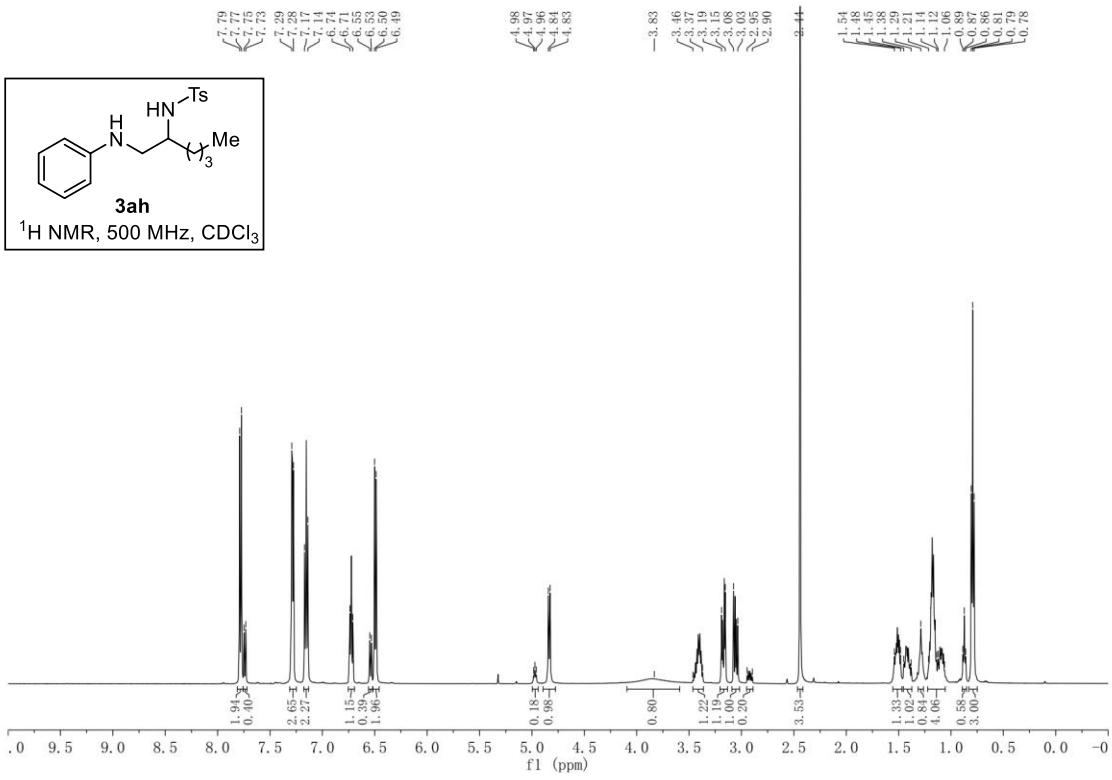
f1 (ppm)
f1 (ppm)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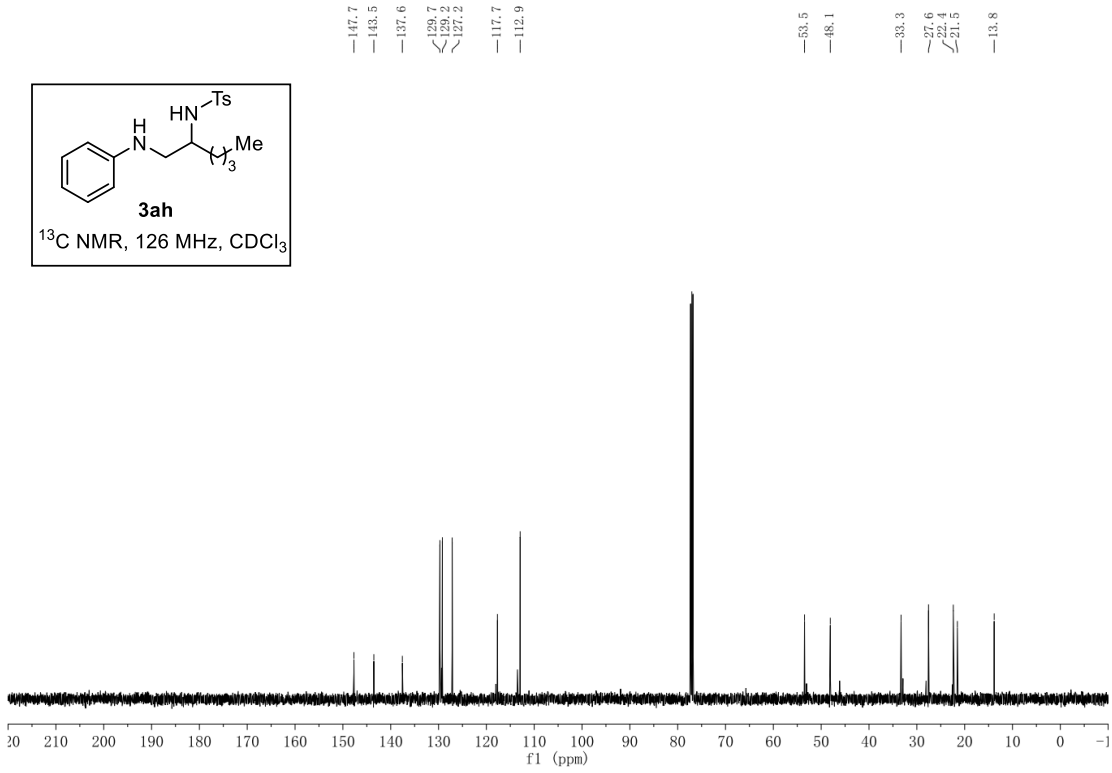
f1 (ppm)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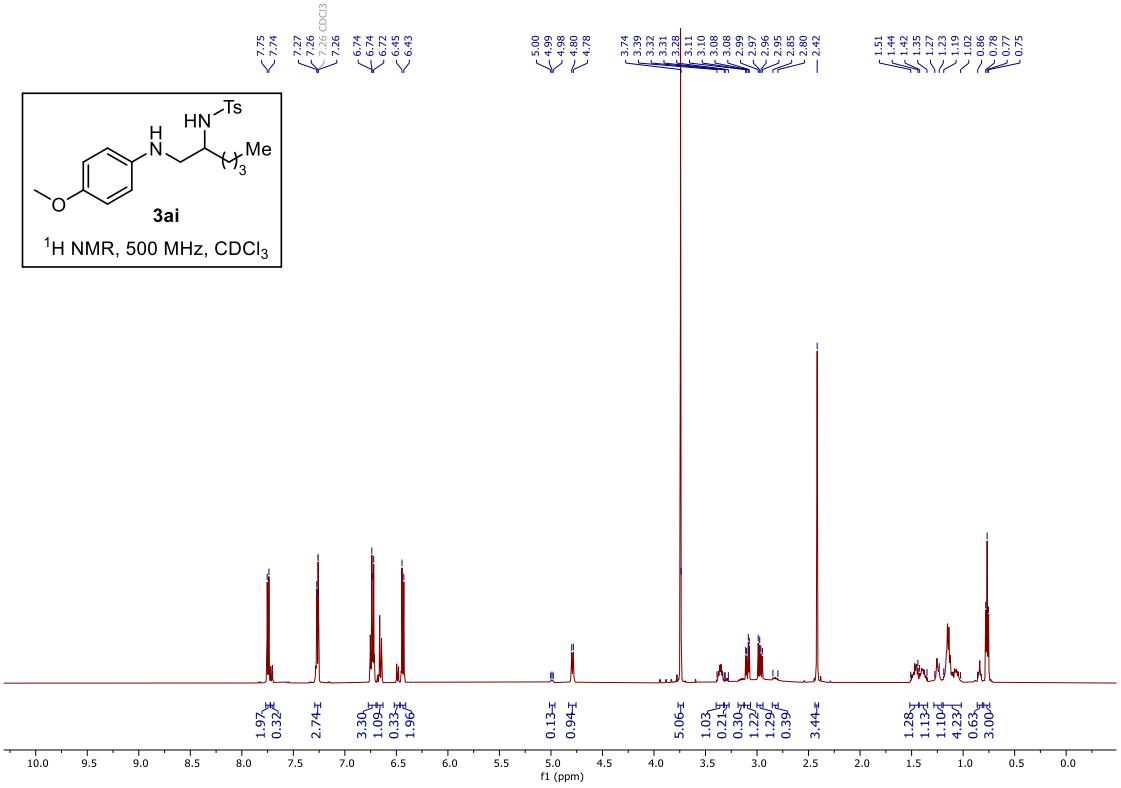
^{13}C NMR, 126 MHz, CDCl$_3$
f1 (ppm)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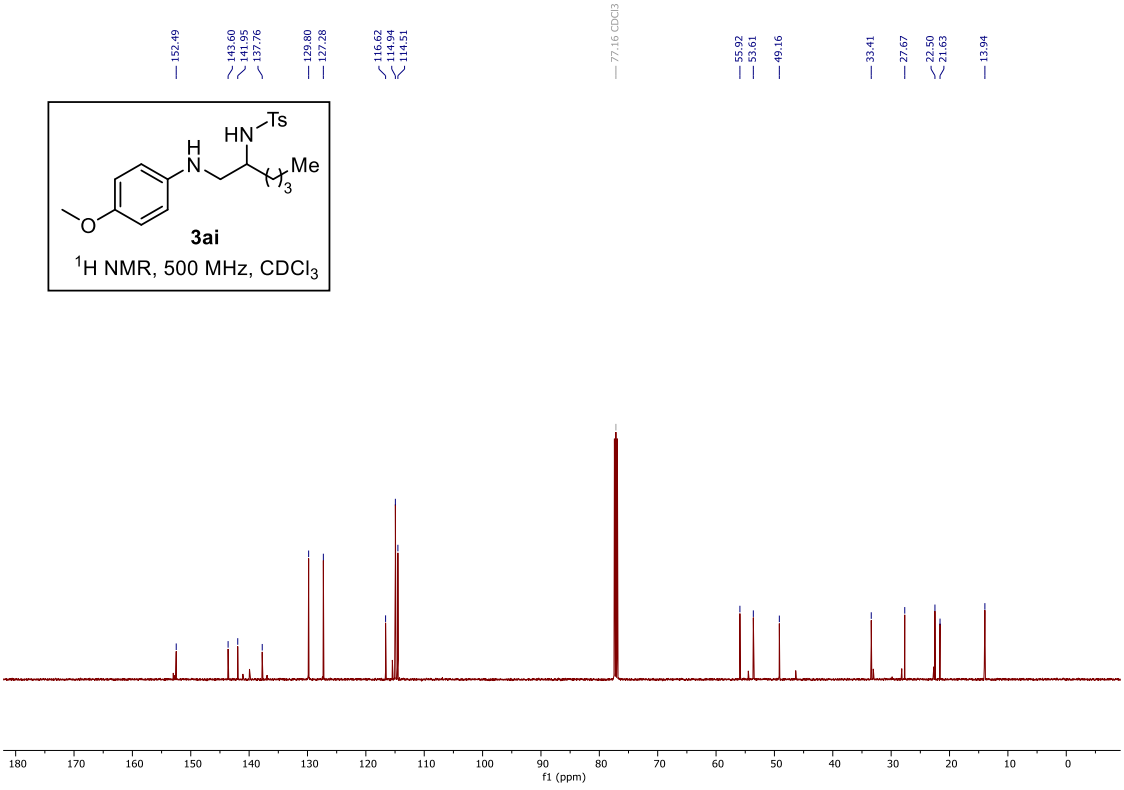
^{1}H NMR, 500 MHz, $CDCl_3$
f1 (ppm)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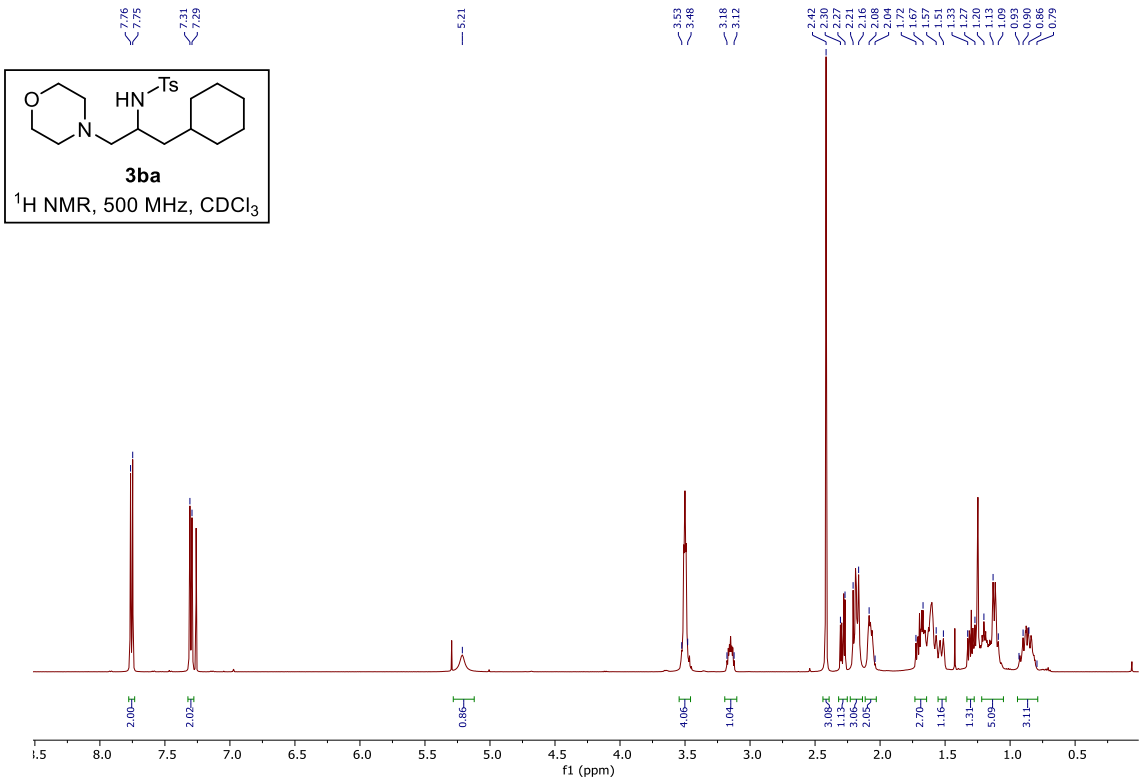
f1 (ppm)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1.57
1.51
1.33
1.27
1.20
1.13
1.08
0.93
0.90
0.86
0.79
O
N
HN
Ts
3ba
1H NMR, 500 MHz, CDCl3
2.00
2.02
0.86
4.06
1.04
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3.06
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2.70
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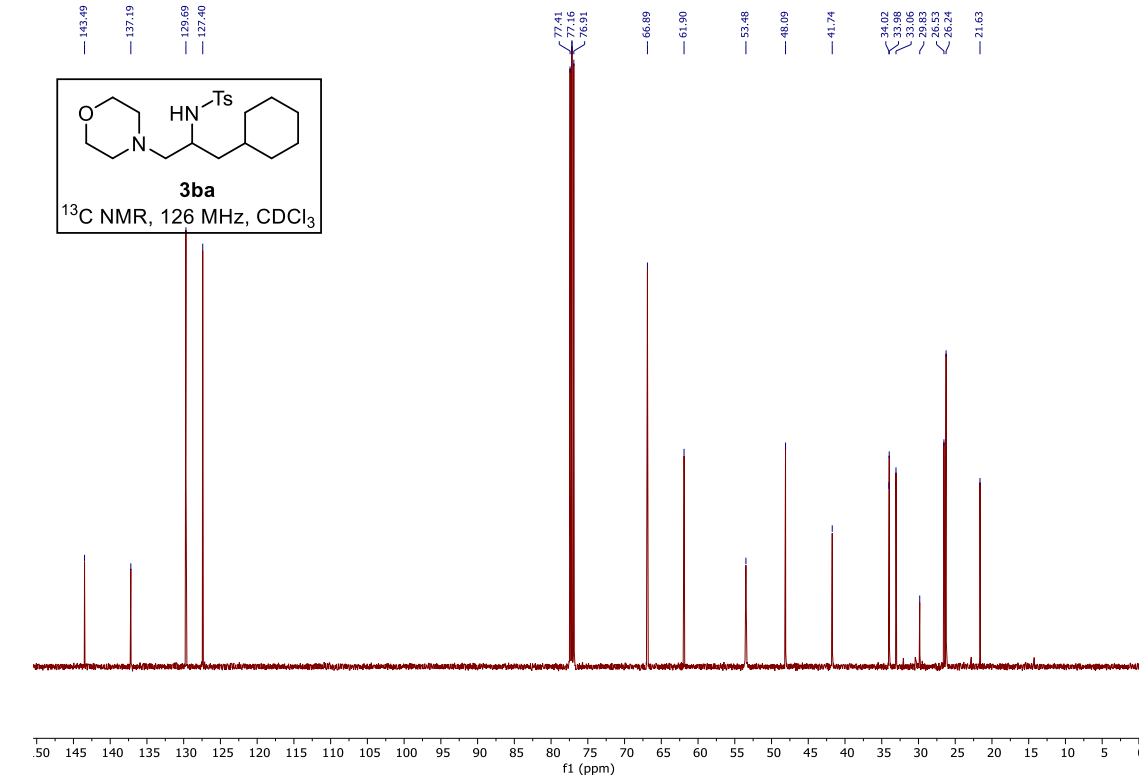
5.09
3.11
f1 (ppm)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34.02
33.98
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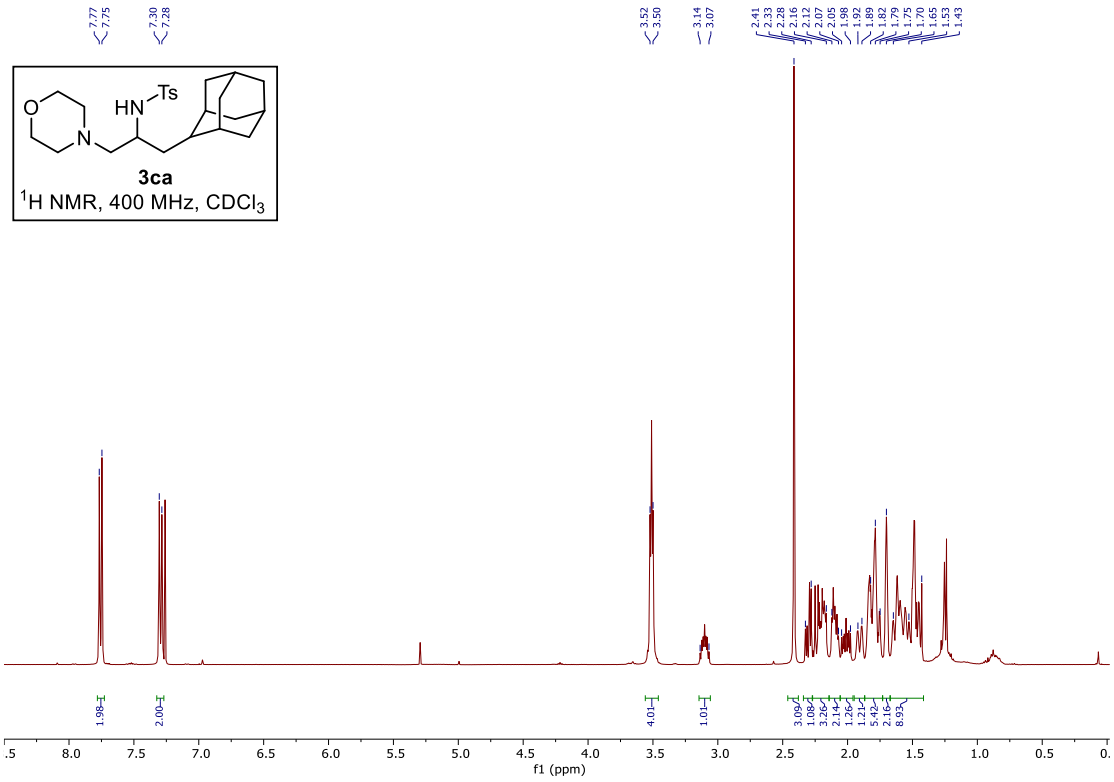
O
N
HN
Ts
3ba
13C NMR, 126 MHz, CDCl3
f1 (ppm)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2.12
2.07
2.05
1.98
1.92
1.89
1.82
1.79
1.75
1.70
1.65
1.53
1.43
O
N
HN
Ts
3ca
1H NMR, 400 MHz, CDCl3
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3.09
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1.26
5.42
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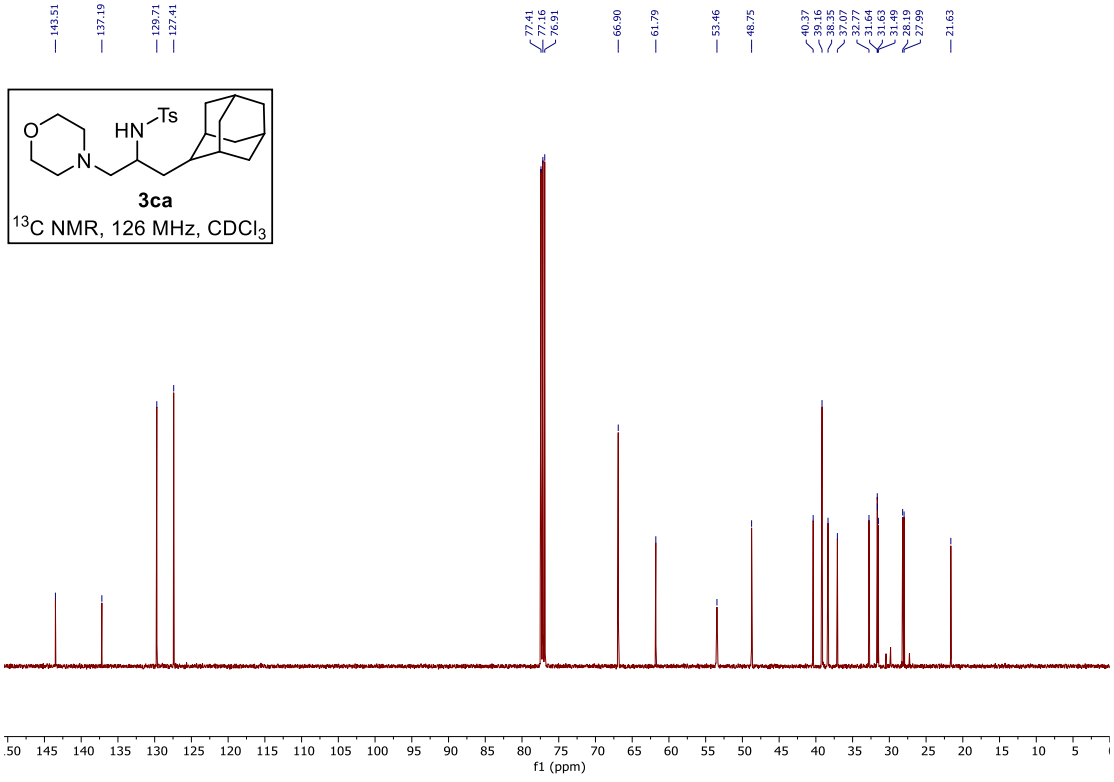
8.93
f1 (ppm)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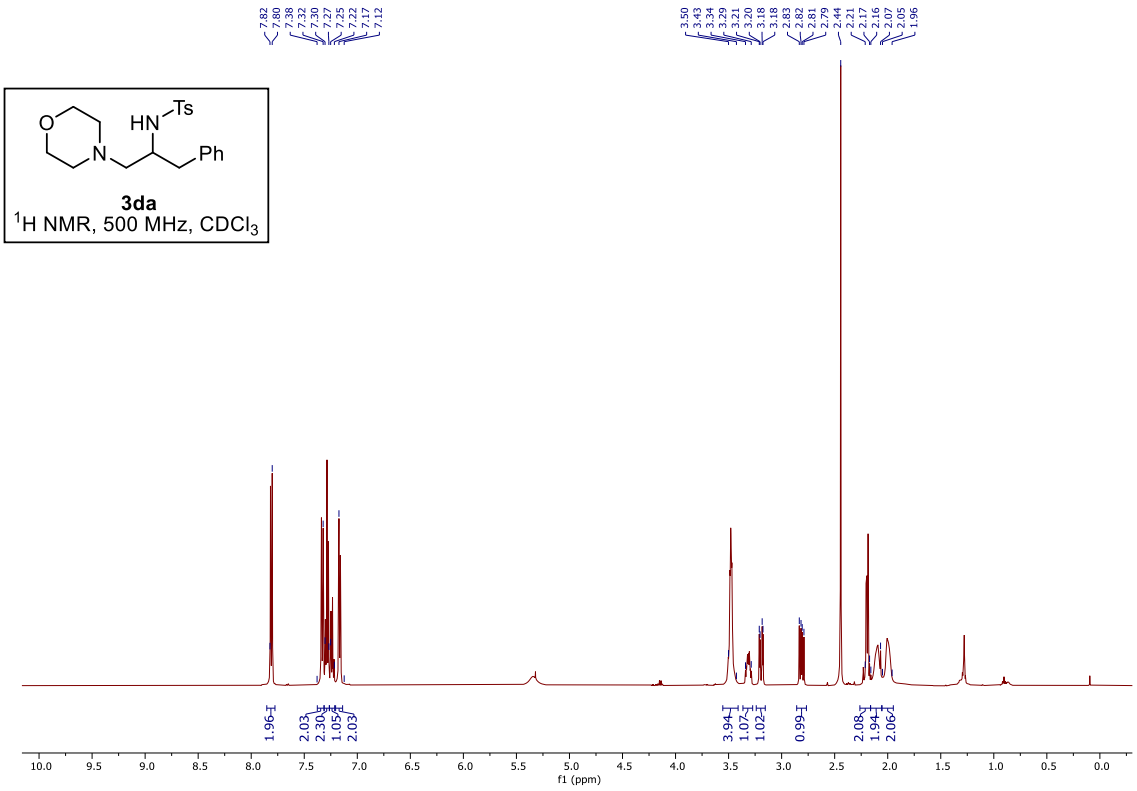
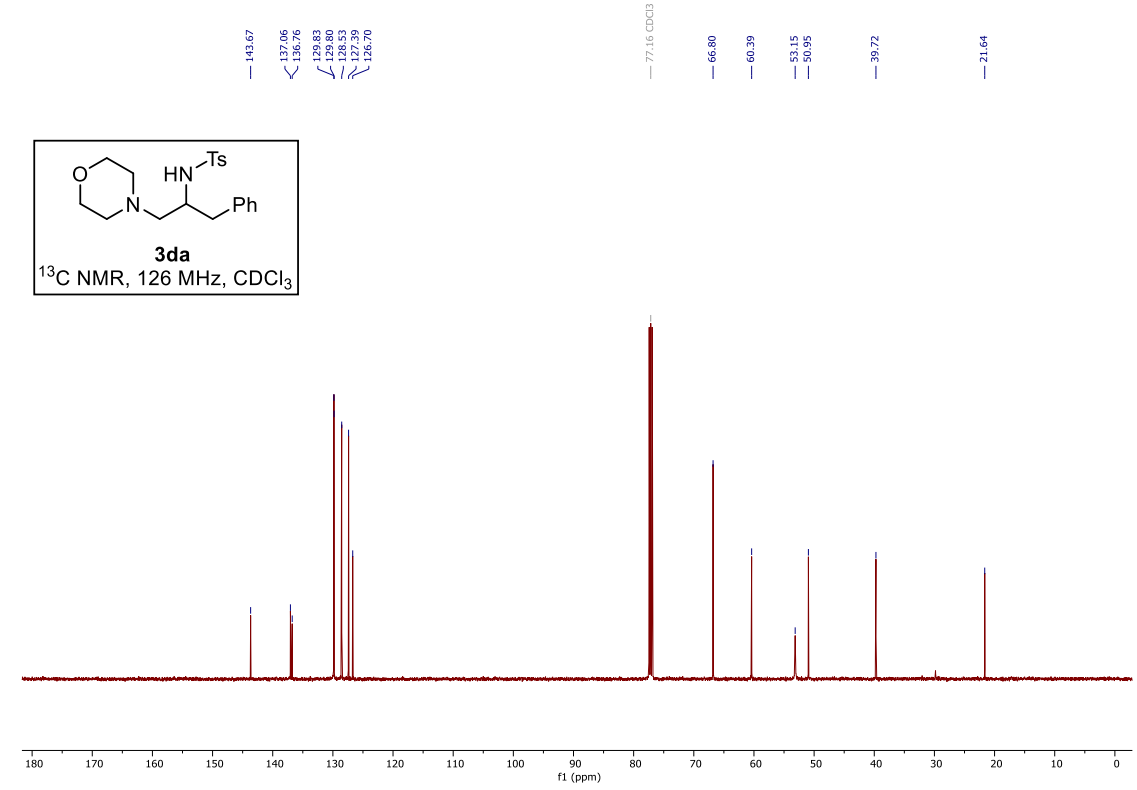
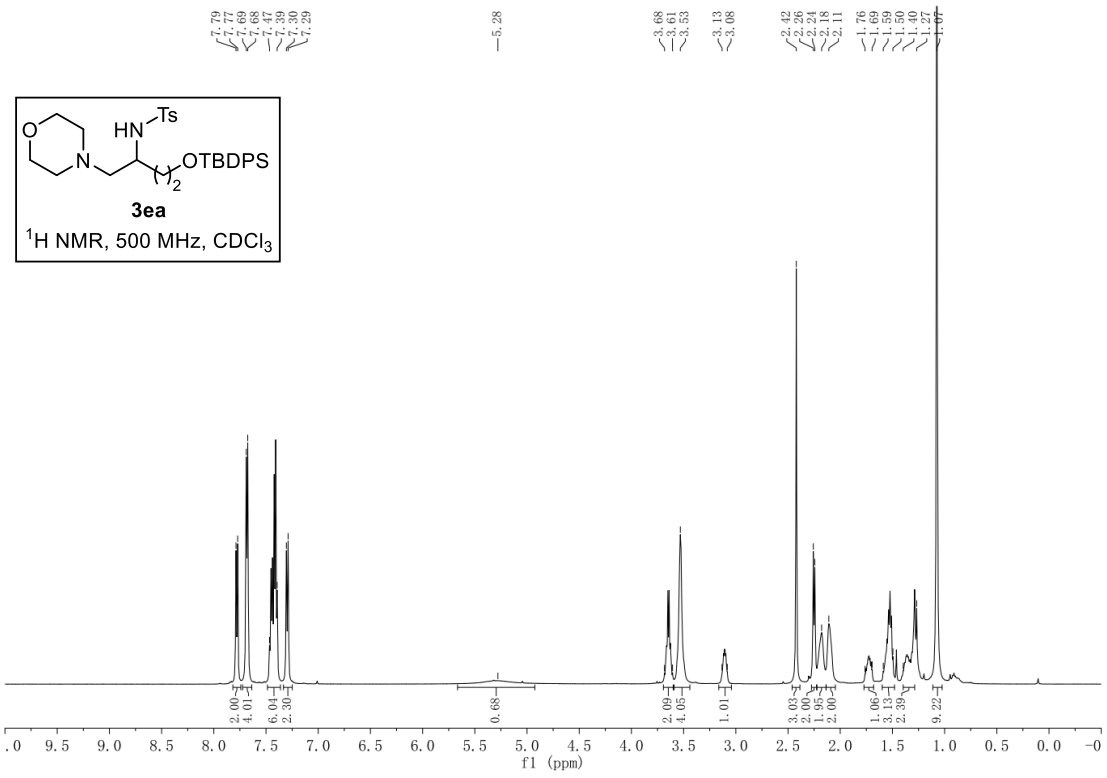
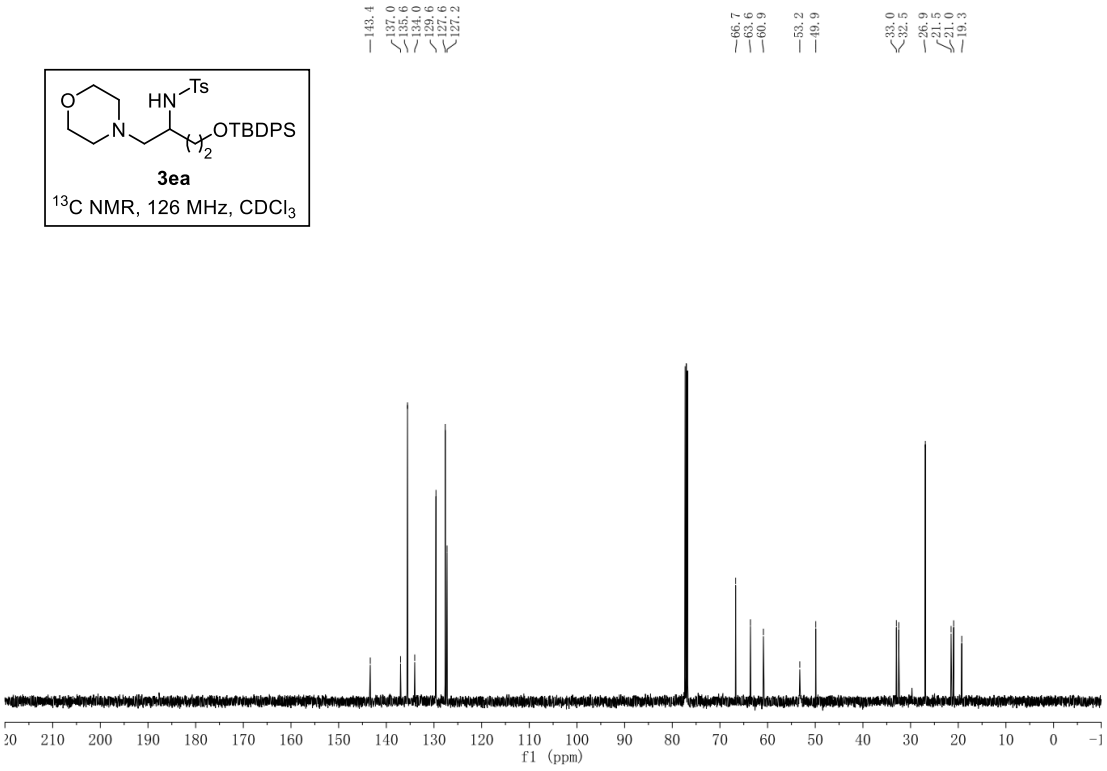
39.16
38.35
37.07
32.77
31.64
31.63
31.49
28.19
27.99
21.63
O
N
HN
Ts
3ca
13C NMR, 126 MHz, CDCl3
f1 (ppm)


Ts
HN
O
N
Ph
3da
1H NMR, 500 MHz, CDCl3
f1 (ppm)

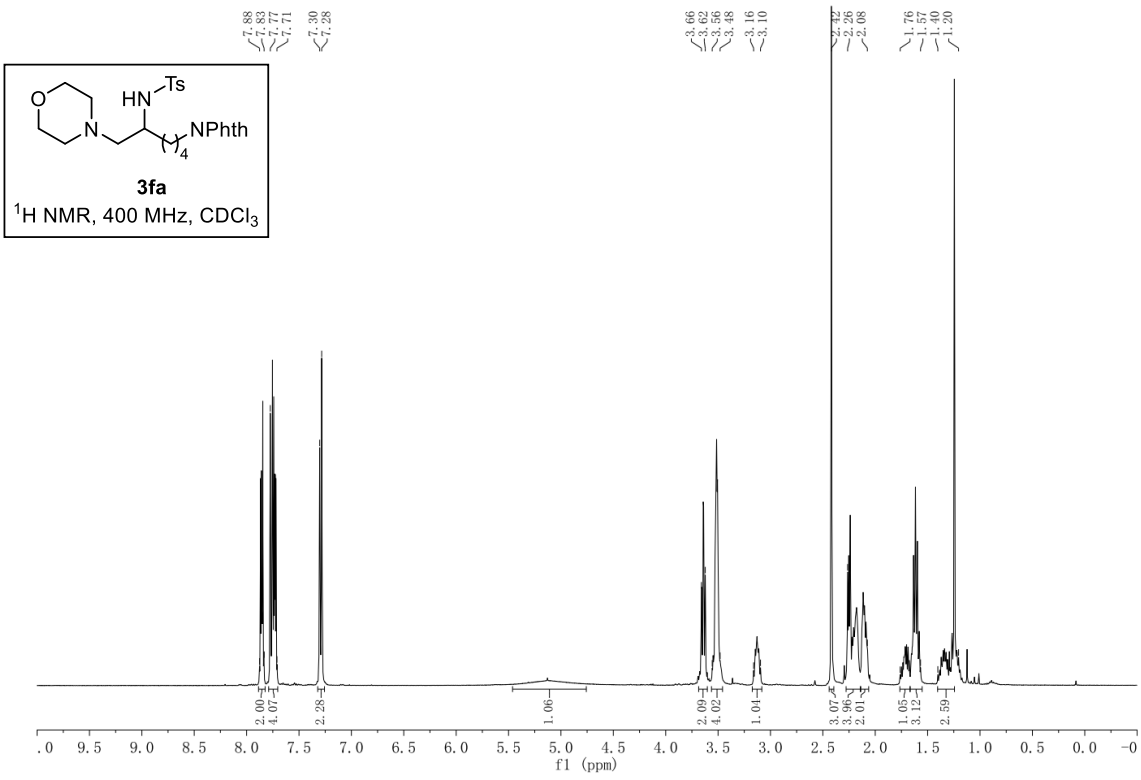

Ts
HN
O
N
Ph
3da
13C NMR, 126 MHz, CDCl3
f1 (ppm)

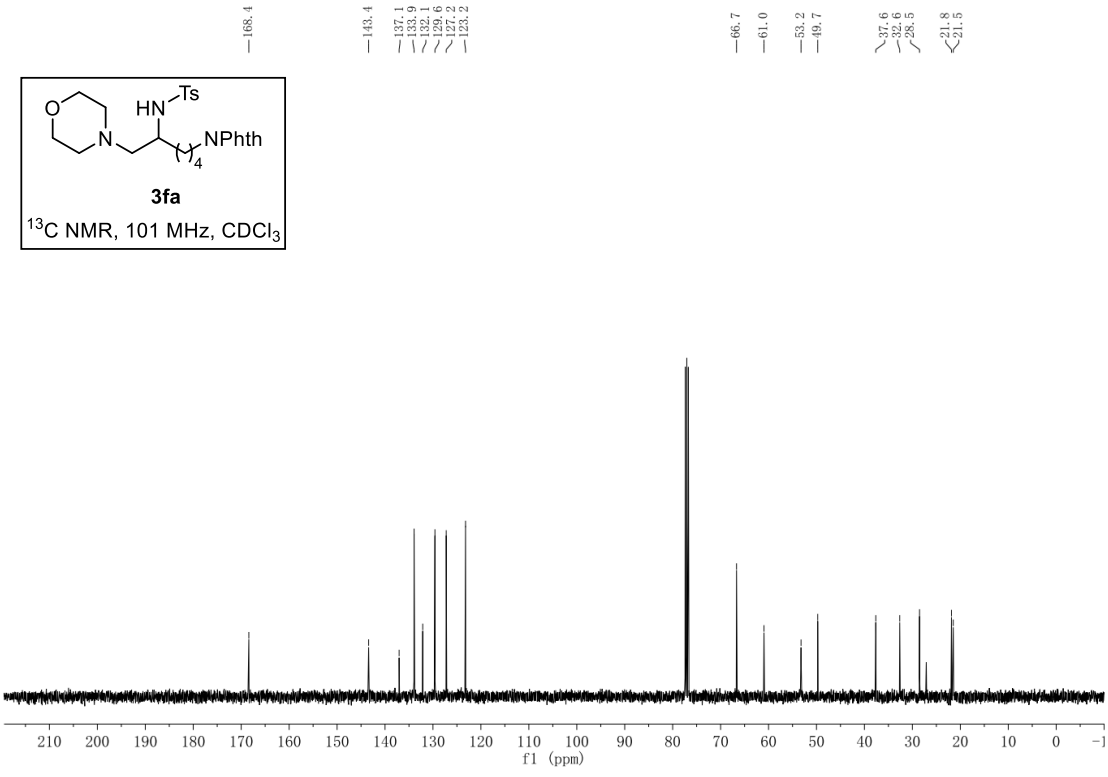

7.79
7.77
7.69
7.68
7.47
7.39
7.30
7.29
5.28
3.68
3.61
3.53
3.13
3.08
2.42
2.26
2.24
2.18
2.11
1.76
1.69
1.59
1.50
1.40
1.27
1.07
2.00
4.01
6.04
2.30
0.68
2.09
4.05
1.01
3.03
2.00
1.95
2.00
1.06
3.13
2.39
9.22
f1 (ppm)

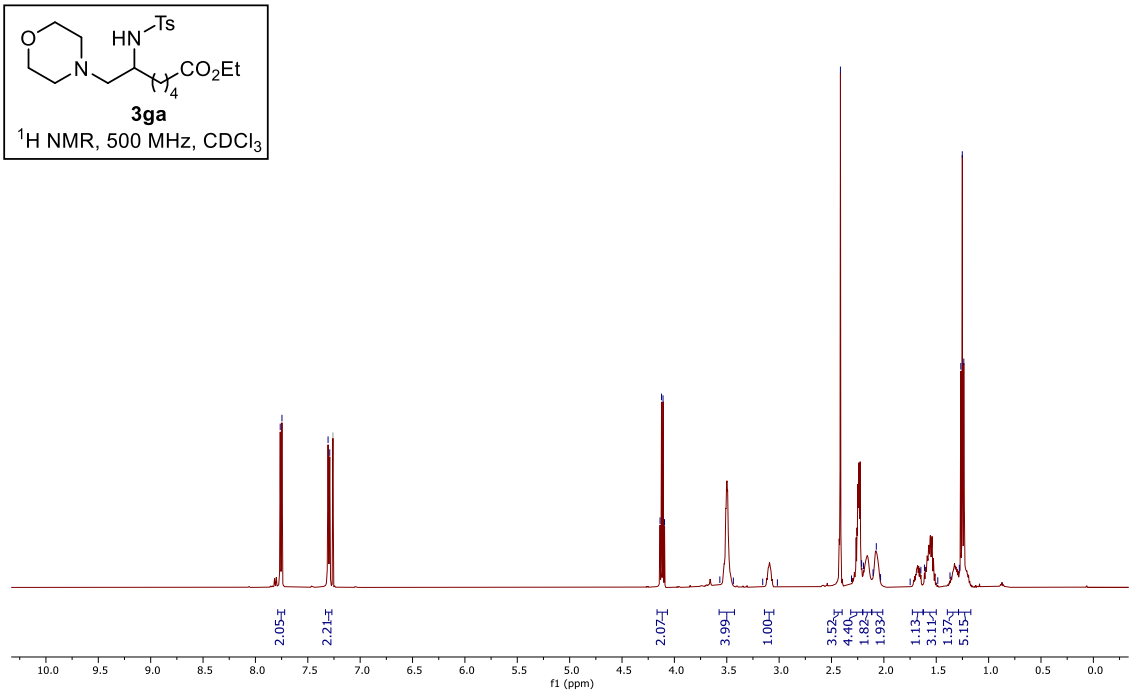
Ts
HN
O
N
OTBDPS
2
3ea
1H NMR, 500 MHz, CDCl3

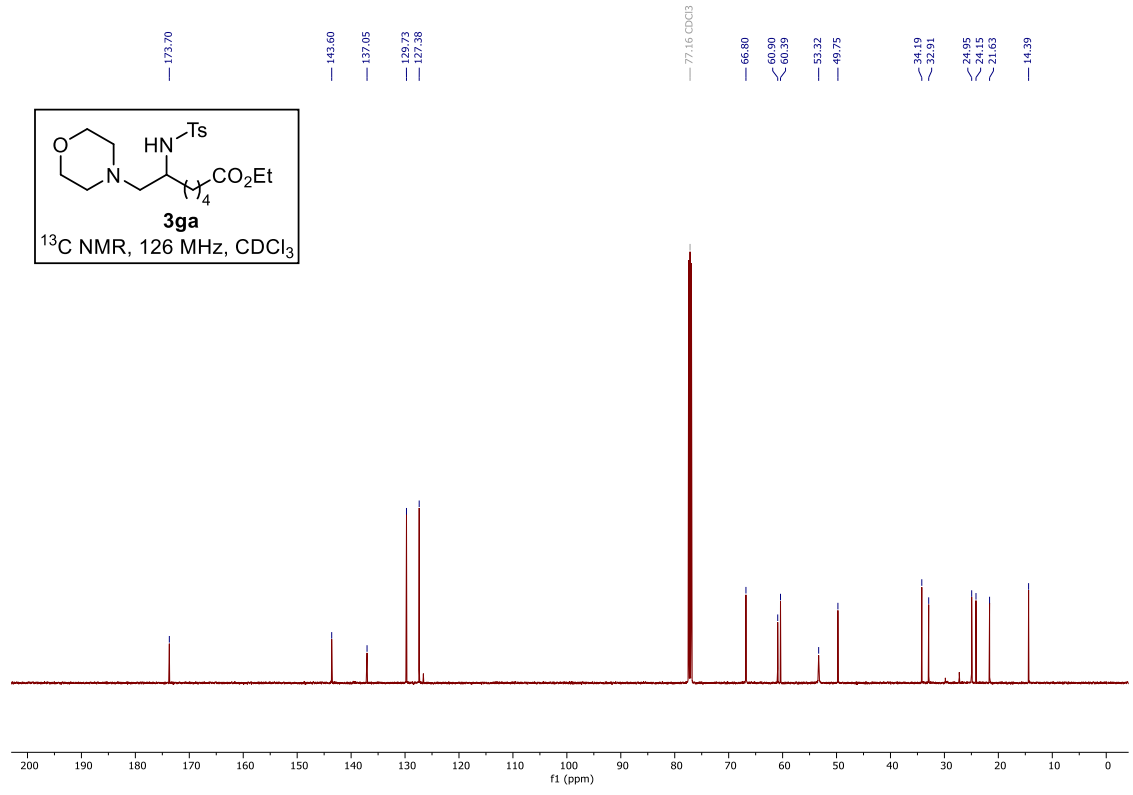

143.4
137.0
135.6
134.0
129.6
127.6
127.2
66.7
63.6
60.9
53.2
49.9
33.0
32.5
26.9
21.5
21.0
19.3
f1 (ppm)

Ts
HN
O
N
OTBDPS
2
3ea
13C NMR, 126 MHz, CDCl3


7.88
7.83
7.77
7.71
7.30
7.28
3.66
3.62
3.56
3.48
3.16
3.10
2.42
2.36
2.08
1.76
1.57
1.40
1.20
Ts
HN
O
N
NPhth
4
3fa
1H NMR, 400 MHz, CDCl3
2.00
4.07
2.28
1.06
2.09
4.02
1.04
3.07
3.96
2.01
1.05
3.12
2.59
f1 (ppm)


168.4
143.4
137.1
133.9
132.1
129.6
127.2
123.2
66.7
61.0
53.2
49.7
37.6
32.6
28.5
21.8
21.5
Ts
HN
O
N
NPhth
4
3fa
13C NMR, 101 MHz, CDCl3
f1 (ppm)


3ga
1H NMR, 500 MHz, CDCl3
f1 (ppm)


3ga
13C NMR, 126 MHz, CDCl3
f1 (ppm)